# UNDERSTANDING CARDIOMYOPATHIES

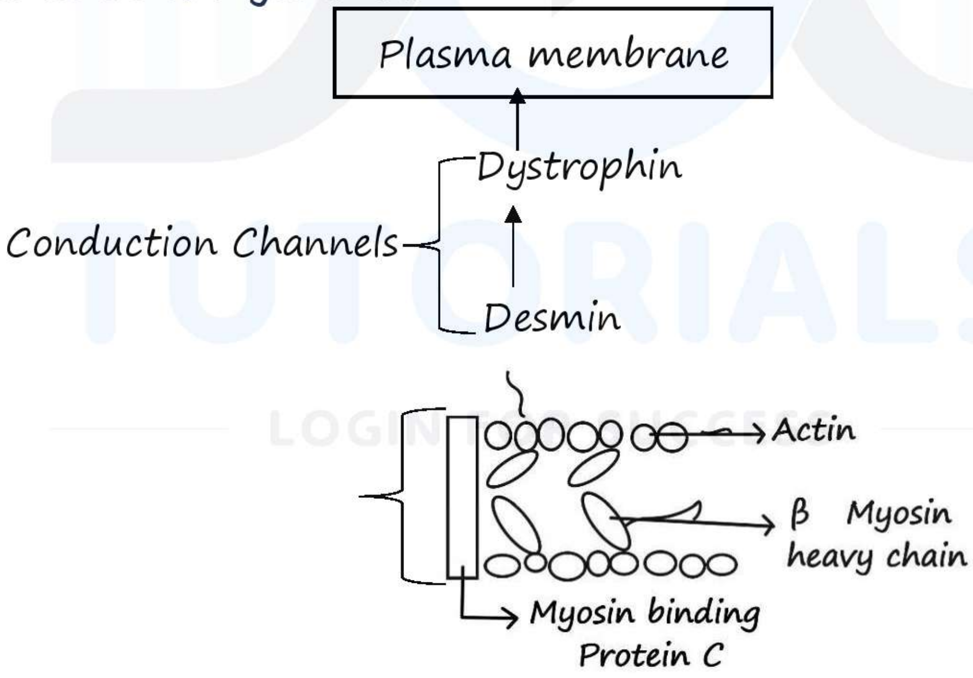
## Cardiomyopathies 00:00:40

**The disorders which affect Myocardium of heart**

Cardiomyopathies

- Intrinsic defects in Myocardium → 1° Cardiomyopathy
- Myocardium id affected due to systemic disorders → 2° Cardiomyopathy

**Structure of myocardium**


Plasma membrane
Dystrophin
Conduction Channels
Desmin
Actin
β Myosin heavy chain
Myosin binding Protein C

- Defect in sarcomere → Seen in HOCM
- Defect in Conduction channels → seen in DCM
- Infiltration into Myocardium → Seen in RCM

# Types of Cardiomyopathies 00:10:30

Types of cardiomyopathies

DCM

HOCM

RCM

DCM

Dilated cardiomyopathy

↓

Dilation of the 4 chambers of Heart

↓

Causes **systolic dysfunction**

HOCM

Hypertrophic obstructive cardiopathy

- Symmetrical Hypertrophy of Interventricular spectrum

Septal thickness

LV wall thickness

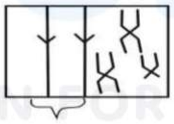
Normal LV thickness 1.5 cm

Normal RV thickness 0.5 cm

Banana shaped left Ventricular cavity on gross examination

microscopy -

Myocyte Disarray



Angulated Myofiber

↓

Myocyte Disarray

↓

Halter skelter Myocyte disarray

Myocyte

- M/C Mutation →

Ⓝ β Myosin heavy chain mutation

- M/c cause of sudden death in younger patient
- **Diastolic dysfunction**

RCM

Restrictive cardiomyopathy

- Infiltration condition due to
  a. Amyloidosis
  b. Sarcoidosis
  Storage disorders
  d. Hemochromatosis
  e. Radiation
- **Diastolic dysfunction**

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# DILATED CARDIOMYOPATHY

- Type of systolic dysfunction due to defect in conduction channels
- Seen in 25-4-year-old

Causes of DCM

Genetic    Other

## Genetic

- M/c Autosomal dominant – M/C mutation is of Titin gene (largest -gene) → 25-40%
- XLR – Mutation is dystrophin gene (usually accompanies patient
- with Becker's or Duchene myopathies
- Mitochondrial inheritance – mutation of β oxidation usually seen in children

## Others

i. Toxic Cardiomyopathy
   - M/c Alcohol- Alcoholic Cardiomyopathy is type of DCM
   - Cobalt
   - Catecholamines – Takatsubo Cardiomyopathy
   - Cocaine
   - Drugs e.g., Doxorubicin (Anthracycline drugs)

## Takatsubo Cardiomyopathy /Broken Heart Syndrome

Stress /Heart Break → Increase Catecholamine's

Left Ventricle Outflow Obstruction

Myocyte Injury

Ischemia (because coronaries Are Also affected)

- Discovered in Japan

Takotsubo cardiomyopathy (fishing pot for trapping octopus)

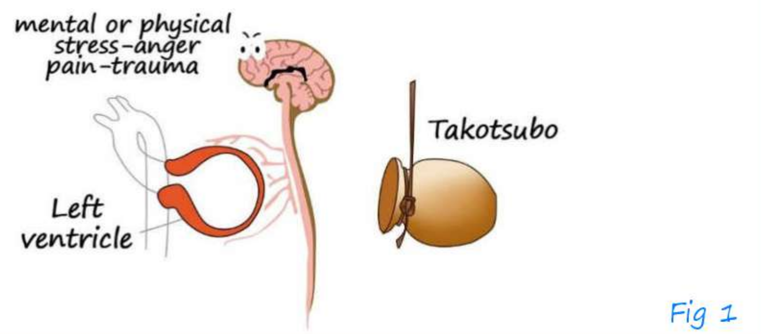


Fig 1

Apical part Bulges

(Because majority of Adrenergic receptors Are present at apex)

↓

Appears like an octopus

Trap used in Japan

↓

Thus named Takatsubo cardiomyopathy

On microscopy – 1) contraction band necrosis

2) Myocyte damage

- Cocaine affects coronaries – causing coronary obstruction dilated CM

ii. Myocarditis

- Inflammation of Myocardium
- Usually due to coxsackie B virus
- Post myocarditis – there is defect in force generation Machinery of heart causing DCM

iii. Peripartum CM

- Type of DCM
- Occurs in late pregnancy -III rd. Trimester or within 1st 6 months of delivery
- Usually more in multiparous females approximately 30-year-old
- Causative agent prolactin

iv. Hemochromatosis

- DCM > RCM

## Causes of DCM

- Genetic -M/C titin mutation (AD)

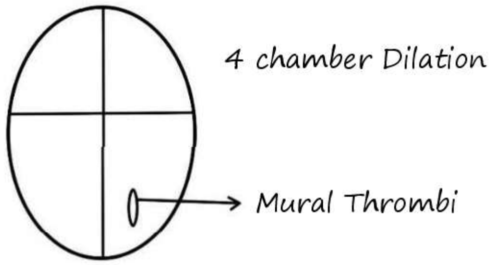
– P ↓ Peripartum

M ↓ CM Myocarditis

T ↓ Toxins → Alcohol

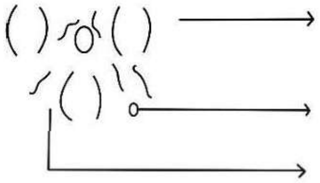
Toxins → Doxorubicin

Gross



Bulky and globular heart

**Microscopy of DCM**



1) Hypertrophied cardiac Muscle fiber
2) Atrophied cardia muscle Fiber
3) Interstitial fibrosis Appears blue on Masson Trichrome stain (stain for collagen)

## Differentials of Globular Heart 00:21:23

- DCM
- Wet Beri Beri
- Syphilis

## Cor-Bo vinum 00:22:18

- Very bulky heart
- Seen in 3° syphilis
- Enlargement of LV due to volume overload

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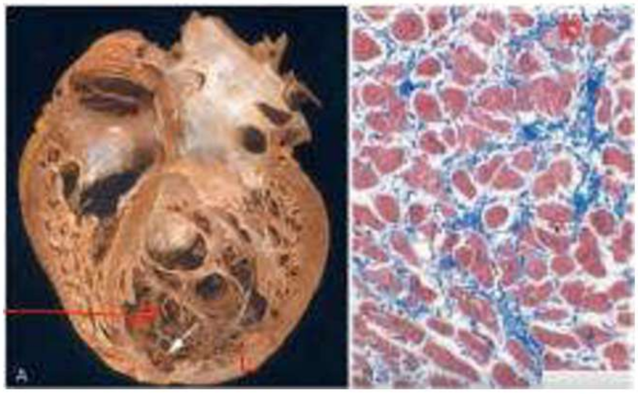
**Anthracyclines** → Toxic causes of DCM

- Microscopy – Vacuolization of myocardium



Dilated cardiomyopathy Fig 2

# RESTRICTIVE CARDIOMYOPATHY

- Also known as Infiltrative cardiomyopathy
- Diastolic dysfunction

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## Causes 00:00:42

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**Cause of RCM**

| | |
|---|---|
| i. Amyloid | i. Loeffler's end myocarditis |
| ii. Radiation | ii. fibroelastosis |
| iii. Haemochromatosis | iii. Endo, myocardial fibrosis |
| iv. Metastasis | |
| v. Storage disorders | |

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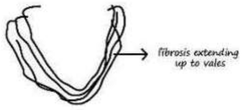
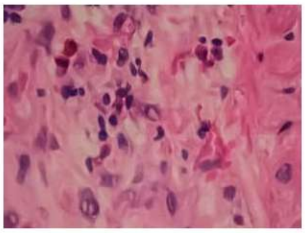
| **I Loffler's endomyocarditis** | **Fibroelastosis** | **Endomyocardial Fibrosis** |
|---|---|---|
| Infiltration of eosinophils<br>In myocardium<br>Eosinophils<br>Major basic protein<br>↓<br>Myocardial necrosis<br>↓<br>Usually associated with PDGDEA/B | • Typically seen in children < 2 years<br>• Deposition of fibroblasts and elastic tissue in endo-myocardium<br>• Cause<br>1. Viral infections eg mutation mumps | •Can occur in children and young adults of African descent<br>•Fibrosis usually occurs in LV extends up to valves<br> |

| | | |
|---|---|---|
| ↓<br>Seen commonly with chronic myeloproliferative neoplasms (CHPN)<br> | 2.Mutation of Tafazzin gene | |

## Hypersensitivity myocarditis

- Closest differential of Loeffler's Endo myocarditis
- Infiltration of Eosinophils in myocardium but no myocardial necrosis
- M/C caused by drugs

## Amyloid causing RCM

- Waxy deposit
- Start in sub endocardium
- Deposit around blood vessels → Ischemia
- Deposition around conduction system → Arrythmia
- on Congo red dye, it will appear in apple green color

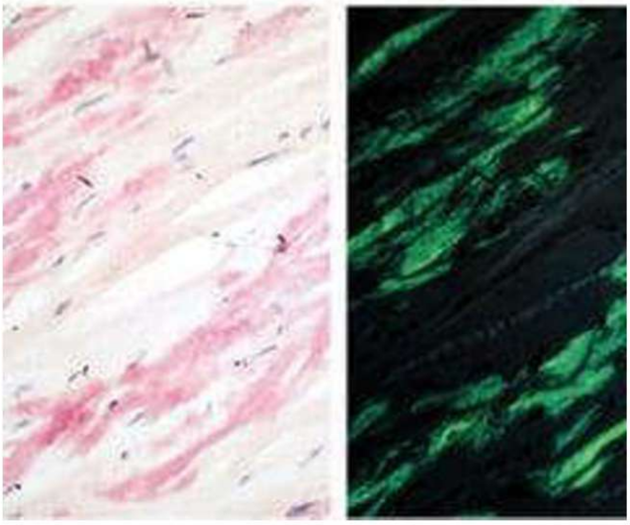


Fig: 1

# ARRYTHMOGENIC RIGHT VENTRICULAR

- Autosomal Dominant
- Defect in gene encoding Desmosomes

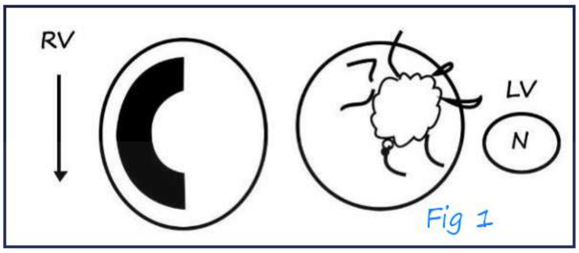


Fig 1

Fibro -fatty tissue starts infiltrating between cells of R.V
due to
defect in Desmoglein 2
↓
So, RV muscles is replaced by fact (yellow tissue)
↓
Hear becomes flabby prone to arrythmias
↓
Arrhythmogenic right Ventricular cardio myopathy

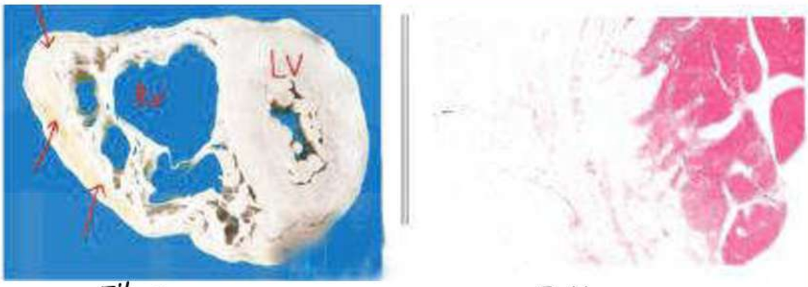
- Intercellular desmosomes
  - Plakophilin
  - Plakoglobin
  - Desmoplasia
- Can also be defective I ARVC
- M/C defect in ARVC= Plakophilin defect
- Desmoplakin defect causes Biventricular ARVC

**Mutation in Plakoglobin** → NAXOS syndrome

i. Hyperkeratosis of hand & feet

ii. ARVC

iii. Wooly hair



Fibro
↓
Appears blue
On Masson trichrome

Fatty
↓
appears pale

Fig 2

# RHEUMATIC HEART DISEASE

## Rheumatic Fever 00:00:17

- Type II Hypersensitivity reaction occurring as a delayed sequel to Pharyngeal injection with group A β-hemolytic streptococci

### Pathogenesis

i. Antigenic cross reactivity

↓

β-Hemolytic streptococci → Sore Threat

M proteins in heart

AB

ii. Ag- APC → T cells

↓

CD4

↓

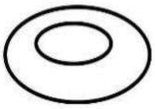
$TH_1$ Cells

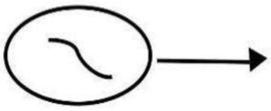
↓

IFN gamma

↓

Macrophages → Activated Macrophages





Anitschkow cells

Caterpillar like chromatin

↓

ASHOFF BODY/NODULE

- Hallmark of Rheumatic heart diseases
- Asch off Body /Nodule around blood vessels

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## Diagnosis: 00:10:27

### Modified JONES Criteria a 2015

| High risk population | Low risk population |
|---|---|
| - Areas of poor economic conditions overcrowding and housing<br> | < 2 cases /1 lakh children /year<br>- Age group most susceptible is 5-15 years |

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### Major Manifestation

| J | O | N | E | S |
|---|---|---|---|---|
| Joint Involvement<br>M/c Major | Carditis | Nodules | Erythema Marginatum | Sydenham's chorea |

### Minor Manifestation (Pneumonic -FEAP)

- Fever
- Raised ESR
- Arthralgia
- Prolonged PR interval

## For Diagnosis

- 2 major

  Or

- 1 major +2 minor with features of pre-existent streptococcal infection

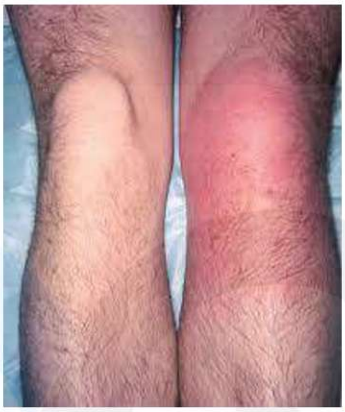

Fig 1

- Migratory polyarthritis of large joints
- M/C involved are large joints of the extremities
- Migratory involvement or flitting nature is characteristic

## Subcutaneous Nodules

- Small, pea sized, painless nodules over bony prominences
- Common sites -Extensor tendons of hands & feet, elbows
- Skin over them is not inflamed

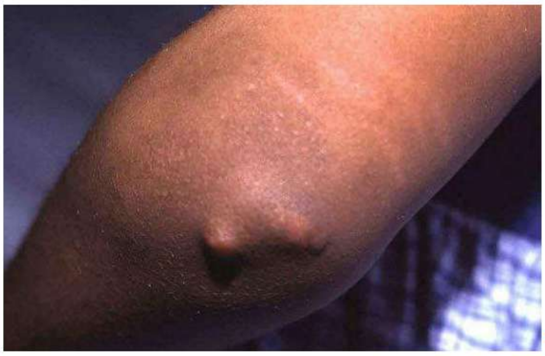

Fig 2

## Erythema Marginatum

- Erythematous rashes with a clear center and round or serpiginous margins
- Transient, Migratory, non-pruritic, and blanch on pressure
- Most commonly seen on the trunk and proximal parts of extremities, but never on face

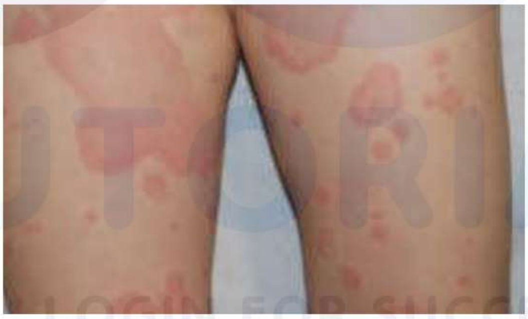

Fig 3

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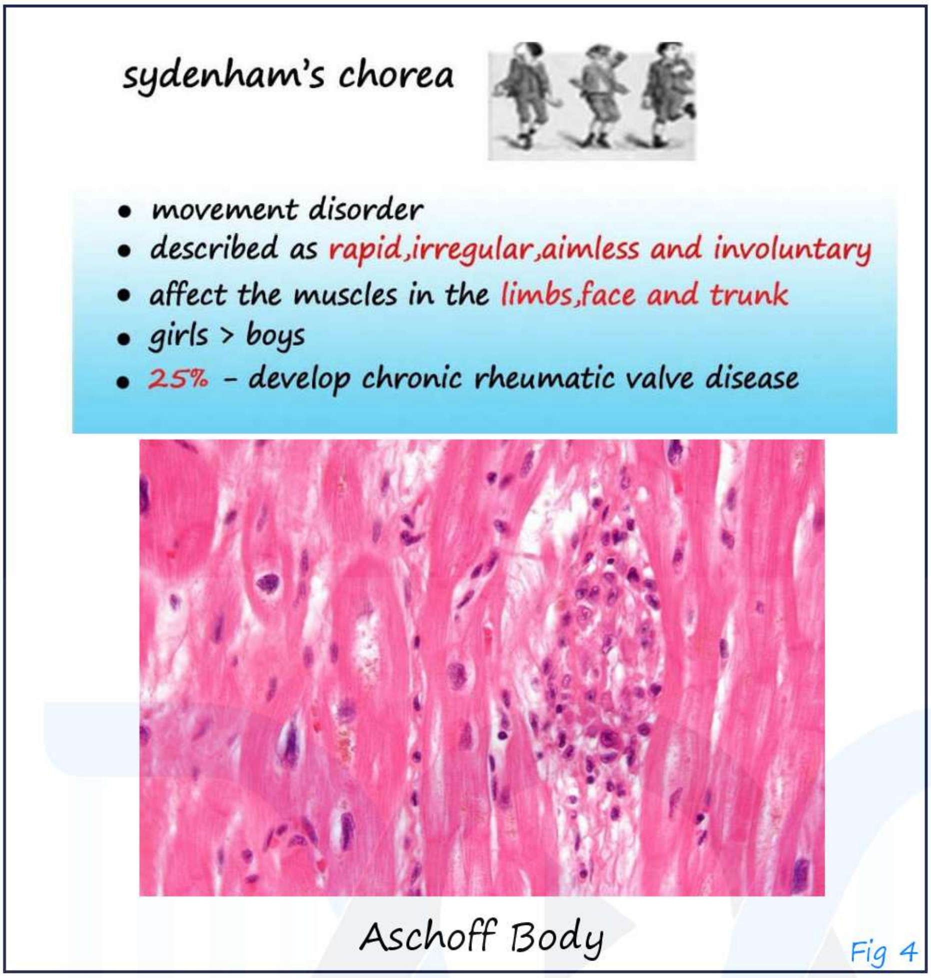

sydenham's chorea

- movement disorder
- described as rapid,irregular,aimless and involuntary
- affect the muscles in the limbs,face and trunk
- girls > boys
- 25% - develop chronic rheumatic valve disease

Aschoff Body

Fig 4

## Hallmark of RHD

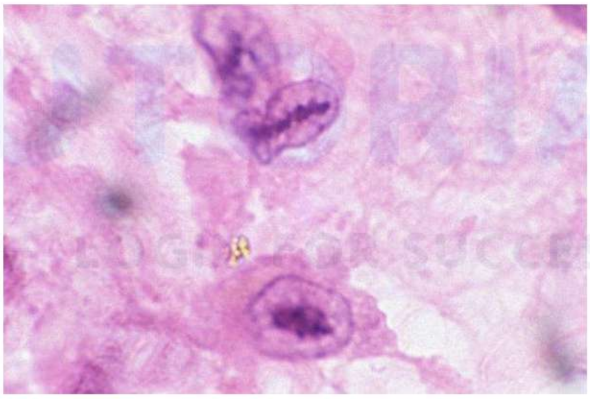

Fig 5

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Hallmark of RHD

- Anitschkow cells showing caterpillar chromatin
- On Transverse section -OWL eye Appearance of nucleus

- Remember -OWL eye inclusion – CMV infection

OWL eye Nuclei:

i. Hodgkin's Lymphoma

ii. Transvers section of anitschkow cell

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## Manifestations of Rheumatic Heart disease

00:24:53

PANCARDITIS

Endocardium
i. Asch off Nodules +

Myocardium
Asch off Nodules + +
M/C seen in Myocardium Near The blood vessels

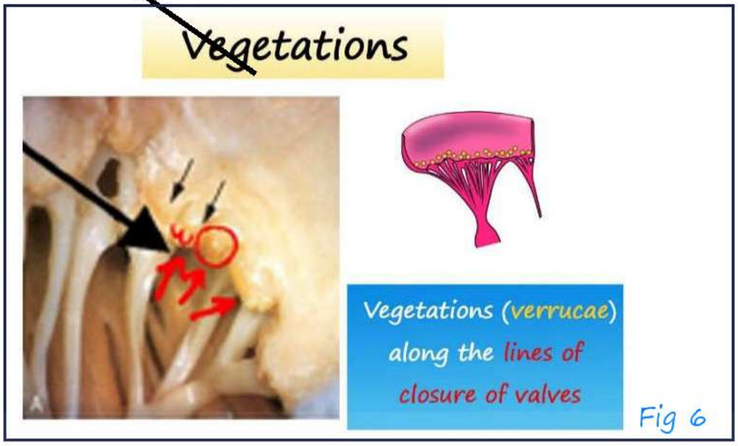
Pericardium
Asch off Nodules+

ii. Verrucae pathogenesis → Activation of platelets & fibrin

- Damage to endocardium  Platelets +fibrin deposition

iii. Degeneration of collagen / swollen collagen
↓
Formation of warty vegetation

- Warty vegetation along the lines of closure of valves



Vegetations

Vegetations (verrucae) along the lines of closure of valves

Fig 6

## Myocarditis

- Asch off Nodules near BV

↓

Myocarditis

↓

Cardiac Failure

(Causes of Death)

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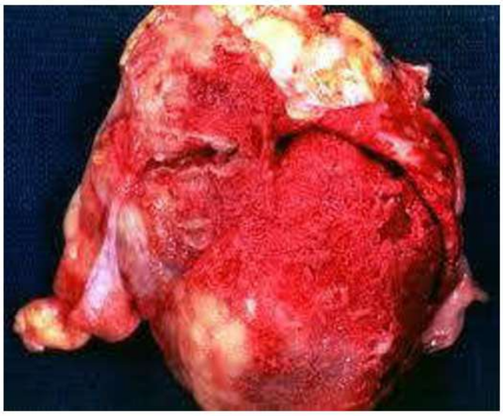
## Pericarditis

- Fibrinous pericarditis

Fibrin depiction between 2 layers of pericardium called as bread & butter pericarditis



Bread & Butter Pericarditis Fig 7

## Manifestation of Chronic RHD 00:30:19

Characterized by fibrosis

**Fibrosis of valves**

i. Leaflet Thickening
ii. Fusion of commissures
iii. Shortening chordae tendinea

**Mac Callum patch**

- Mitral regurgitation causes a roughened patch on the wall of left atria posterior called Mac- Callum Patch
- A Frequent site of Mural Thrombus

Fish Mouth Deformitve of Valve

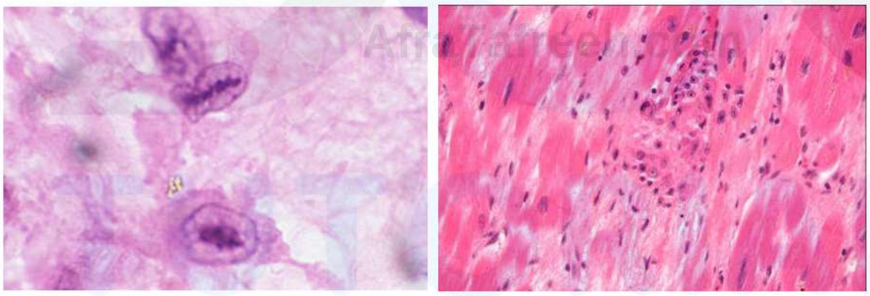


Fig 8

- Mac Callum patch
- Thinned chordae tendinea

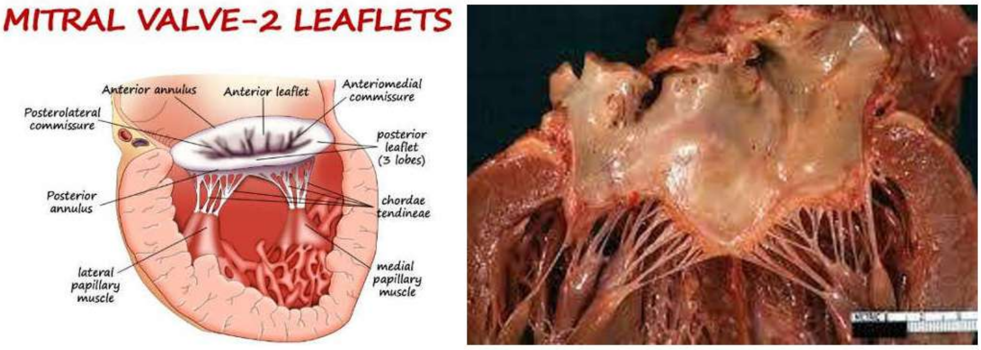
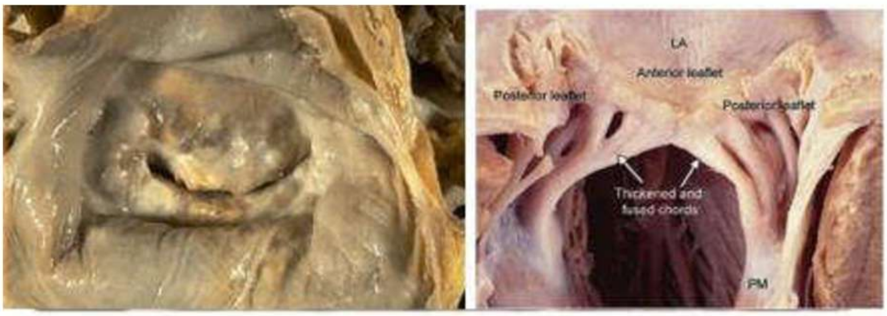

MITRAL VALVE-2 LEAFLETS
Anterior annulus
Anterior leaflet
Anteriomedial commissure
Posterolateral commissure
posterior leaflet (3 lobes)
Posterior annulus
chordae tendineae
lateral papillary muscle
medial papillary muscle

Fig 9


LA
Anterior leaflet
Posterior leaflet
Posterior leaflet
Thickened and fused chords
PM

MITRAL STENOSIS WITH DIFFUSE THICKENING AND DISTORTION OF VALVES

THICKENED CHORDAE TENDINAE

Fig 10

# MYOCARDIAL INFARCTION

## Myocardial Infarction

Transmural infarction
- When > 75% of coronary Arteries blocked especially LAD
- Apex – commonly Affected
- ST Elevation

Subendocardial
- occurs due to
- Occurs due to Plaque Disruption
- NSTEMI

Multifocal Infarction
- Infarction at multiple areas
↓
- progresses into Takatsubo cardio-myopathy

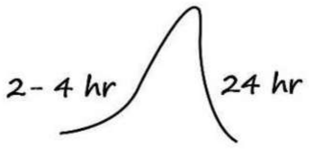
- Subendocardial
  - Most Prone to Ischemia
  - Infarction follows plaque disruption

## Diagnosis of MI 00:03:43

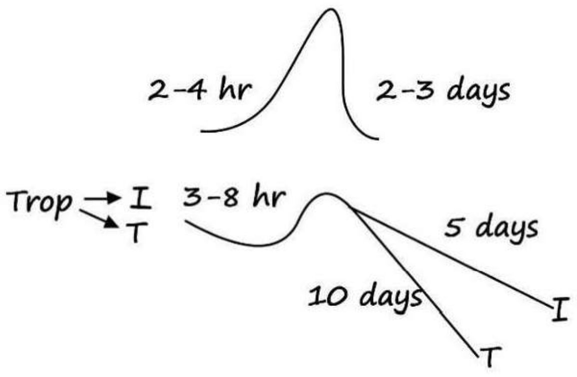
### Diagnosis of MI

Cardiac makers
- Earliest to Rise- Myoglobin

Biopsy /Autopsy
- Reversible injury Seen on E/M till ≤ 30 min



CK-MB



Waviness of
Myocardial fibers
Myocytolysis
↓
Hydropic change
around myocardia
fiber's

**Flipping of LDH**

- Normally ≥ LDH 2 LDH1

  In MI LDH1 ≥ LDH2
- SGOT elevated

---

## Biopsy/Autopsy findings 00:06:42

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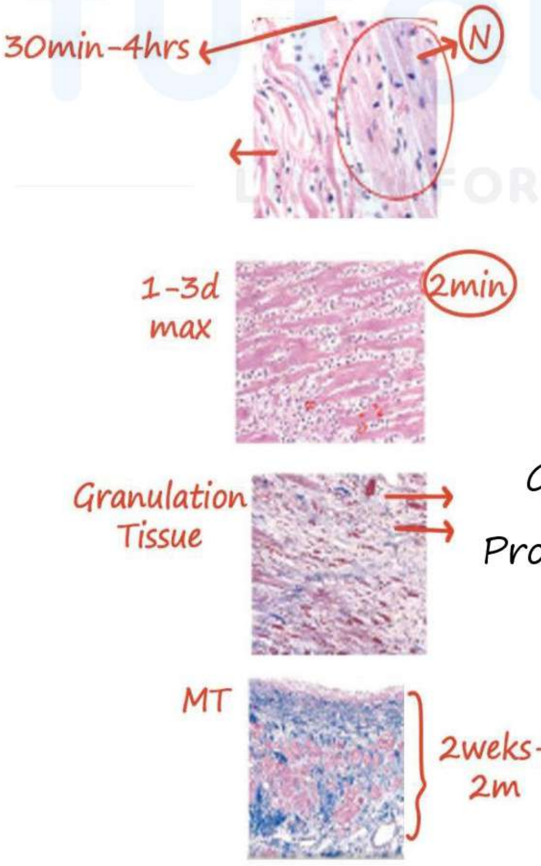
< 30mins-Reverisble change

> 30mins-Irreverisble change

30mins- 4hours: Waviness of myocardial cells

| | |
|---|---|
| 4-12 hrs | - Coagulative Necrosis<br>- On gross-dark mottling |
| 12-24 hrs | - Neutrophils Infiltrate<br>- Myocyte Hyper eosinophilia |
| 1 to 3 days | - Contraction band Necrosis<br>- Maximum Neutrophil (Abscess) |

| | |
|---|---|
| 3 to 7 days | - Gross-Yellow Tan infarct center<br>- Macrophages appear |
| 7 to 10 days | - Gross – Hyperemic border<br>- Granulation Tissue appears |
| 10 to 14 days | - Gross – Hyperemic border<br>- Max Granulation Tissue appears |
| 2wk | - Scarring Starts |
| 2m | - Completion of scarring |


30min-4hrs
N
1-3d
max
2min
Granulation
Tissue
MT
2weks-
2m

Earliest finding – Waviness

30mins-4hours

Neutrophilic infiltration

Granulation Tissue – Proliferating blood vessels

Masson's Trachoma depicting collagen in scar

Fig: 1

## Evolution of Morphological changes in MI

| Time | Gross | Light Microscopy | Electron Microscopy |
|---|---|---|---|
| Reversible injury 0-30 min. | None | None | • Relaxation of myofibrils<br>• Glycogen loss<br>• Mitochondrial swelling |
| **Irreversible injury** | | | |
| 30 min – 4 hr | None | Waviness of fibers at border (earliest microscopic change | • Sarcolemmal disruption<br>• Mitochondrial amorphous densities |
| 4 – 12 hr | Dark mottling appears | Beginning of coagulative necrosis | |
| 12 – 24 hr | Dark mottling | • Neutrophilic infiltration<br>• Myocyte hypereosinophilia<br>• Marginal contraction | |

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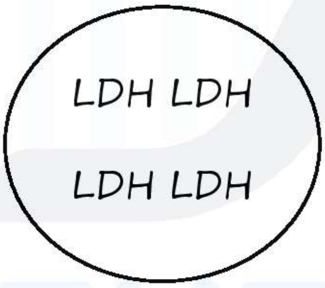
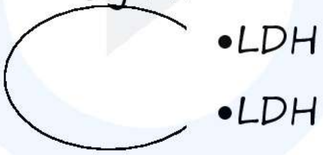
| | | | |
|---|---|---|---|
| | | band necrosis | |
| 1 – 3 days | Yellow tan infarct center | Brisk interstitial infiltrate of neutrophilis | |
| 3-7 days | Hyperemic borders, central yellow tan softening | Marcophages at infarct border | |
| 7 – 10 days | Maximum yellow tan | Early formation of fibrovascular granulation tissue at margins | |
| 10 – 14 days | Red gray infarct border | Well established granulation tissue collagen deposition | |
| 2 – 8 weeks | Gray white scar | Collagen deposition | |

| | | | |
|---|---|---|---|
| > 2 months | Scorring complete | Dense collagenous scar | |

## TTC Triphenyl – Tetrazolium chloride stain

- TTC Stain binds to LDH giving → Manage colour<br>→ Brick Red colour

| Reversible injury | Irreversible injury |
|---|---|
|  <br>- LDH within the cell<br>- Stain Positivity with TTC | Eg MI<br> <br>Membrane Disruption<br>- Loss of LDH<br>↓<br>- No Staining by TTC<br>- Pale heart<br>↓<br>- Infracted Heart<br>- Old infarcts appear glistening white<br>- New infarcts appear Pale |

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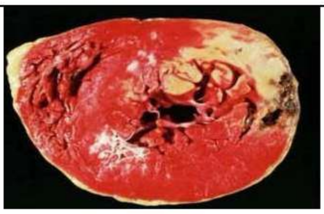
| | |
|---|---|
| |  |

## TTC Results start appearing by 4 hours of Infarction

### REPEREVSION

| | |
|---|---|
| Free Radicals<br>↓<br>Cause stunned myocardium<br>↓<br>(Transient ischemia) | Calcium<br>↓<br>Causes Hypercontraction of heart<br>↓<br>Formation of contraction bands |

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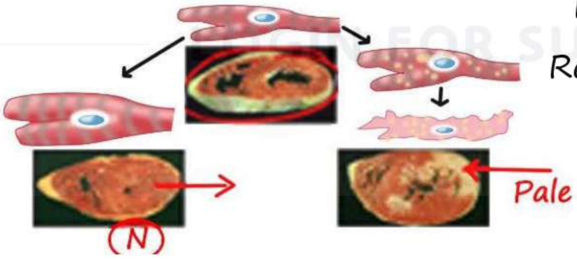
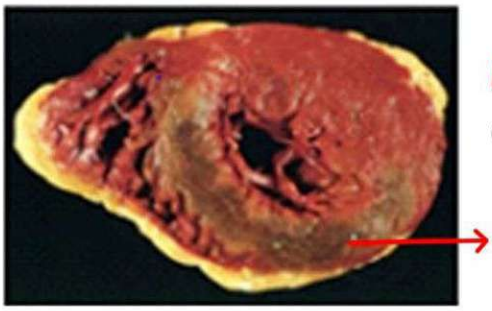
Triphenyltetrazolium chloride,an enzyme substrate that colors viable myocardium magenta failure to stain is due to enzyme loss after cell death



Red infarct in Reperfused heart

Fig: 2



**Reperfused**

Contraction Bands- Sign of Increased Calcium in Myocardial fibrosis

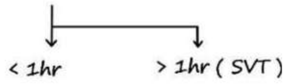
Fig: 3

| Stunned Myocardium | Hibernating Myocardium |
|---|---|
| - Occurs if coronary Blood flow was impaired for a brief period of 5-15 minutes | - Exposure to Chronic, sublethal ischemia |
| - State of Prolonged Cardiac Failure induced by transient ischemia | - Myocardium enters into a state of lowered metabolism and function called Hibernation |
| - Recovers after several days | - Reversible with Revascularization |
| - May follow Reperfusion injury | |

## Complication of MI 00:29:27

Mnemonic: **ACT RAPID**

i. Arrythmia



1.Vascular Tachycardia

2.Contractile Dysfunction – causes Cardiogenic Shock

3.Thrombus (Mural)

4.Rupture – Of Free wall (3rd to 7th day after MI)

- Usually, Anterolateral wall of left ventricle especially at mid-ventricular level

5.Aneurysm – Pseudoaneurysm

6.Pericarditis

- Post MI Pericarditis called as Dressler Syndrome Autoimmune
- Either at 1-3 day of Mi or 1-3 week of MI

7.Infarct Expansion

8.Dysfunction – papillary muscle Dysfunction

# ENDOCARDITIS

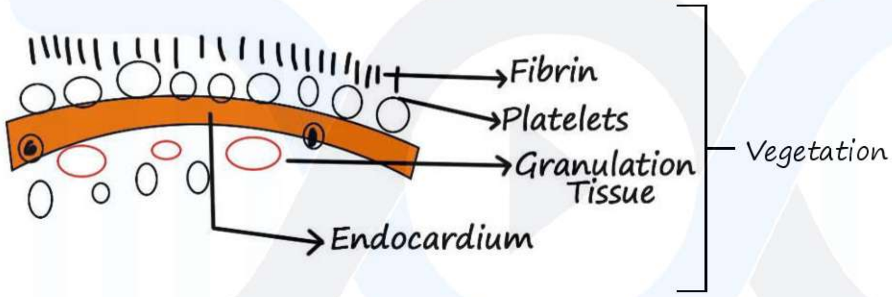
- Inflammation of endocardium

## Pathogenesis

Turbulence of blood flow due to
- VSD, PDA
- MVP
- AR, MR

↓

Damage to Endocardium


Fibrin
Platelets
Granulation Tissue
Endocardium
Vegetation

- If patient with endocardial injury undergoes dental extraction without antibiotic prophylaxis

↓

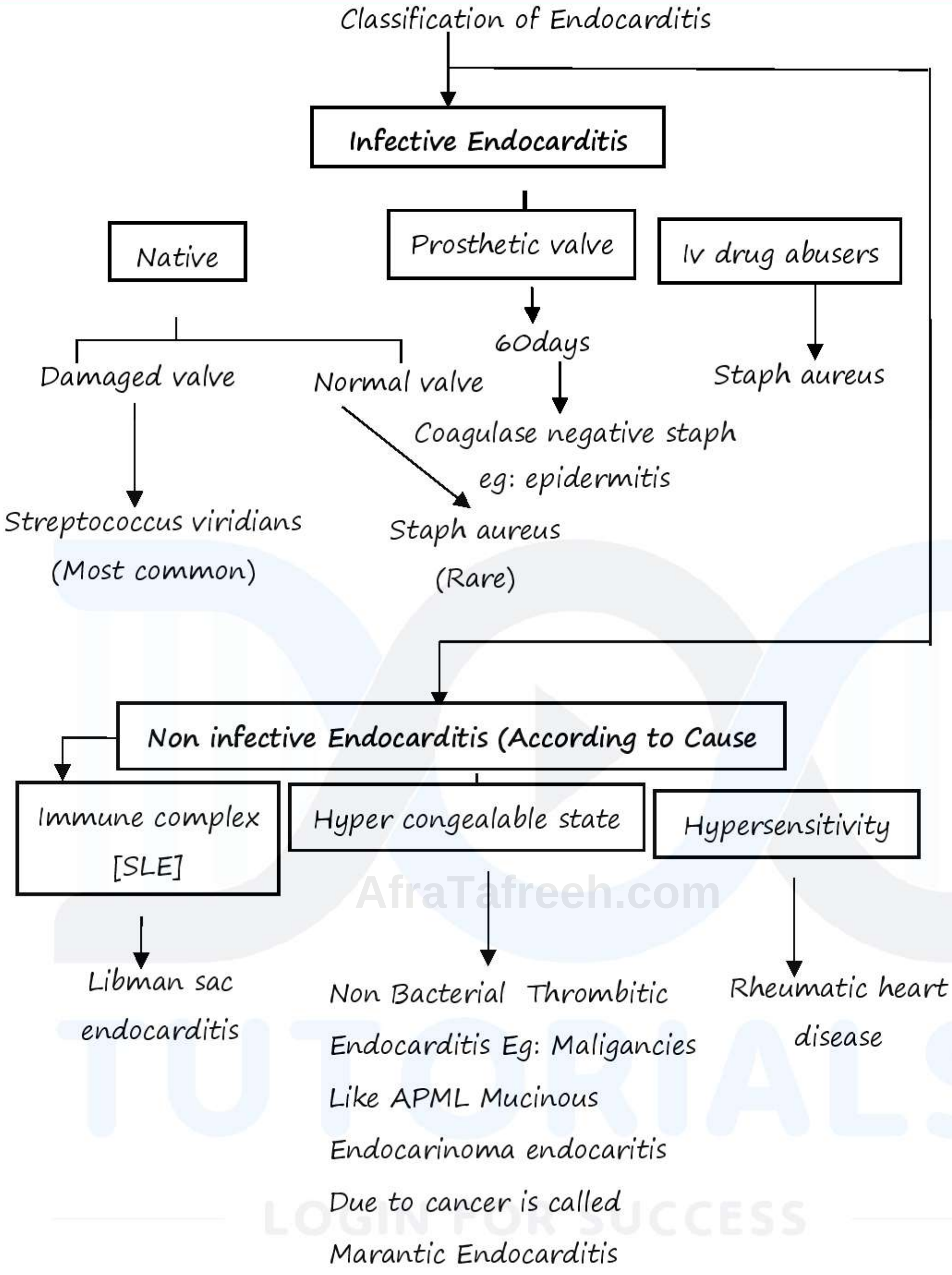
Bacteria lodge into the vegetations

↓

Causing infective endocarditis

- Streptococcus viridians causes subacute endocarditis while staphylococcus aureus (as in I.V drug abusers) causes acute endocarditis

## Classification 00:08:23


Classification of Endocarditis
Infective Endocarditis
Native
Prosthetic valve
Iv drug abusers
Damaged valve
Normal valve
60days
Staph aureus
Streptococcus viridians (Most common)
Coagulase negative staph eg: epidermitis
Staph aureus (Rare)
Non infective Endocarditis (According to Cause
Immune complex [SLE]
Hyper congealable state
Hypersensitivity
Libman sac endocarditis
Rheumatic heart disease

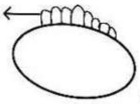
Non Bacterial Thrombitic Endocarditis Eg: Maligancies Like APML Mucinous Endocarinoma endocaritis Due to cancer is called Marantic Endocarditis

DOC TUTORIALS LOGIN FOR SUCCESS

Vegetation

Infective Endicarditis

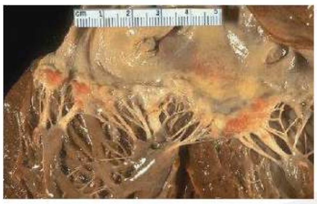
Non infective endocarditis



RHD

Small and wary vegetations

1. Called as verrucae
2. Along the lines of closure
3. Warty vegetations



SLE

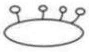
Libman sac Endocarditis

Microscopy:

i. IC damage endothelium of vessels:
ii. fibrinoid necrosis
iii. LE bodies
iv. Hematoxylin bodies

NBTE

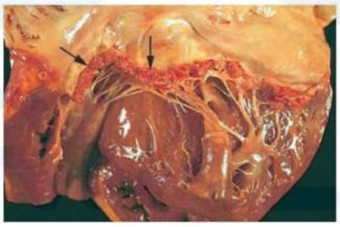
Vegetation along the lines of closure



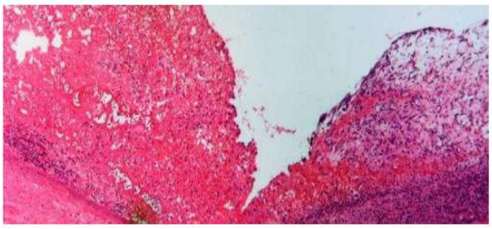
- Multiple vegetation
- Loosely attached to valve
- Do not damage the valve
- High risk of embolization

Microscopy

- Fibrin only
- No inflammation



Complete Row of Vegetations Along Line of



No inflammation

## Infective Endocarditis 00:31:22

- Cause Bacteria
- Fungi

i. Rare

ii. Bigger vegetation

Endocardial injuries
↓
Plt + fibrin
↓
Bacteria:
↓
Inflammatory cells
↓
Release of cytokines

] Bulky vegetation

- Bulky vegetation
- On the valvular surface
- Cause maximum to valves
- Can even extern to chordae, tendinea, papillary muscles, and myocardium
- Extension into myocardium results in ring abscess
- Highest risk of embolization

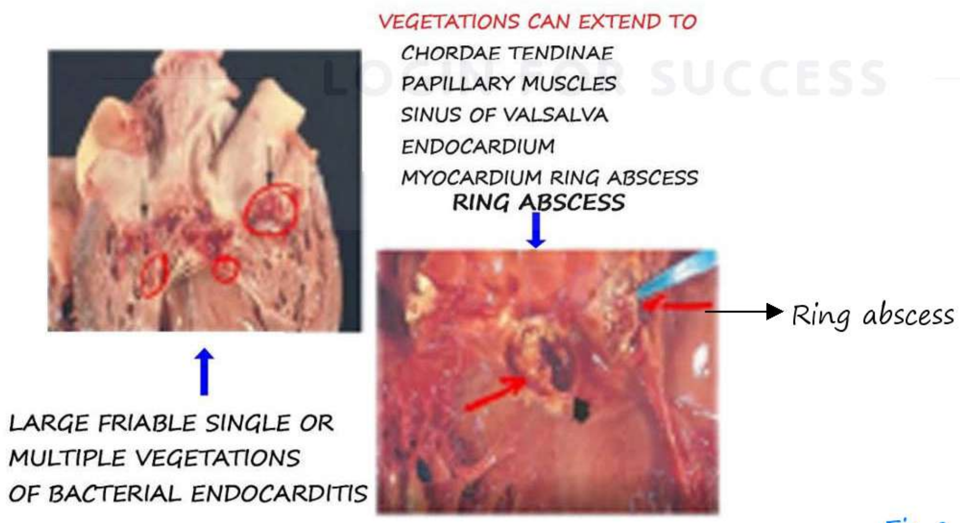

VEGETATIONS CAN EXTEND TO
CHORDAE TENDINAE
PAPILLARY MUSCLES
SINUS OF VALSALVA
ENDOCARDIUM
MYOCARDIUM RING ABSCESS
RING ABSCESS
Ring abscess
LARGE FRIABLE SINGLE OR MULTIPLE VEGETATIONS OF BACTERIAL ENDOCARDITIS

Fig 2

## Diagnosis of IE: 00:37:18

- DUKES criteria
  - Pathological criteria
    - Demonstration on micro - Organism
    - Histopathological confirmation of active endocarditis clinical
  - Clinical criteria
    - Major
    - Minor

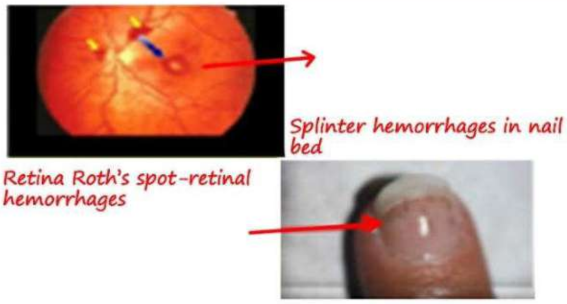
- Major criteria
  - Positive culture
    - Characteristic Organism

      Eg: staph aureus
    - Unusual bacteria persistently positive on 2 Occasion 12 hours apart
  - Echo showing new valve regurgitation

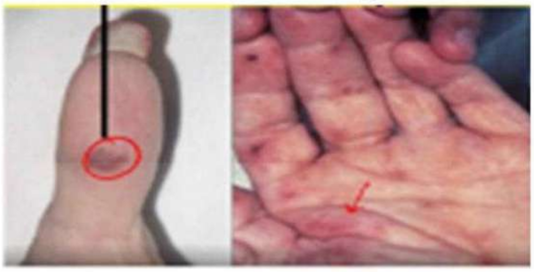
- Minor criteria
  - i. vascular finding
    - septic emboli
    - myotic aneurysms
    - splinter hemorrhages
    - Janeway lesion on palm and soles
  - ii. Immunological
    - Glomerulonephritis
    - Osler's node
    - Roth's spots in retina
    - Rheumatoid factor+
  - iii. Previous history

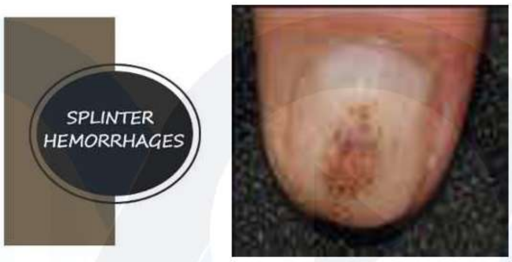
    fever > 38°
  - iv. Microbiological: culture - unusual:
    - organism cultured only one time
  - v. ECHO -charge in intensity on murmur

DCI TUTORIALS LOGIN FOR SUCCESS

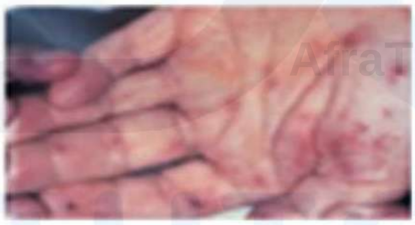

Splinter hemorrhages in nail bed
Retina Roth's spot-retinal hemorrhages

Osler Node Janeway Leison




SPLINTER HEMORRHAGES

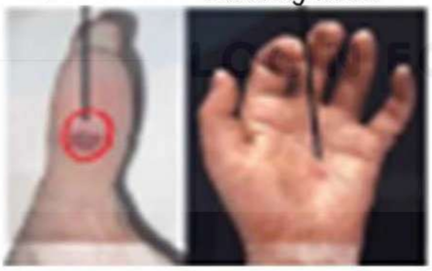
## Janeway lesions



Small erythematous or hemorrhagic,**macular, nontender lesion** on the palms amd soles and are the consequence of septic embolic events

## OSLER NODES

Osler nodes Janeway leison



small,tender subcutaneous nodules that develop in the pulp of the digits or occasionally more proximally in the fingers and persist for hours to sevseral days.

## Duke Criteria

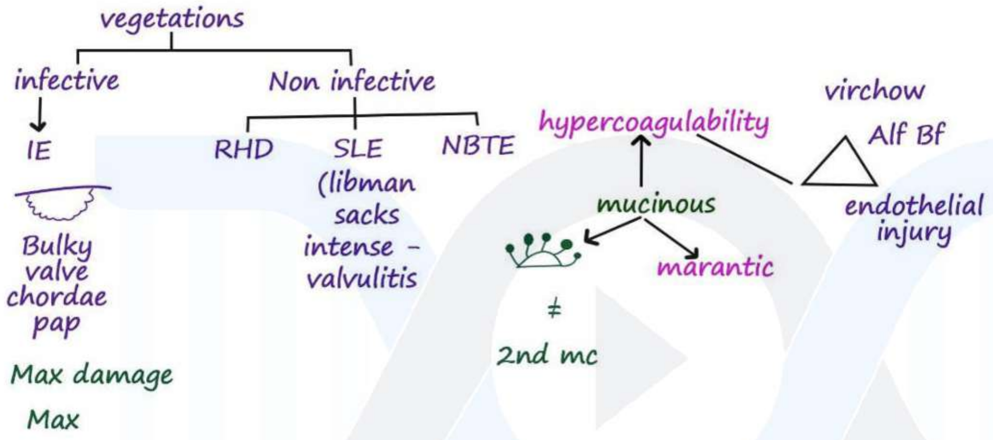
either pathologic or clinical criteria

if clinical criteria are used
2 major,
1 major + 3 minor,
5 minor criteria are required for diagnosis

Fig 2

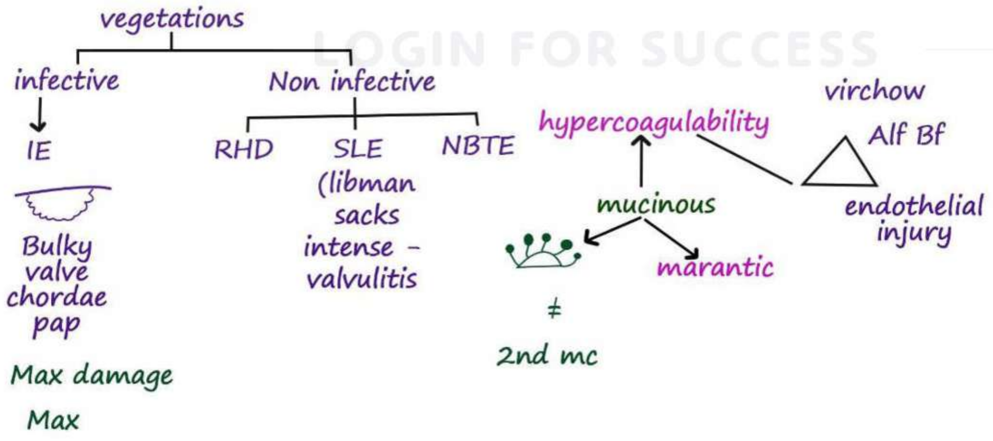
## Risk of factors for IE: 00:49:58

i. Rheumatic heart disease
ii. Congenital heart diseases
iii. Mitral valve prolapses
iv. Asymmetrical septal hypertrophy
v. Intravenous drug abusers


vegetations
infective
IE
Bulky valve chordae pap
Max damage
Max
Non infective
RHD
SLE (libman sacks intense - valvulitis
NBTE
hypercoagulability
mucinous
marantic
≠
2nd mc
virchow
Alf Bf
endothelial injury

## Summary: 00:50:42

- M/V involved valves -Mitral & Aortic
- Tricuspid valve commonly involved in IV drug abusers

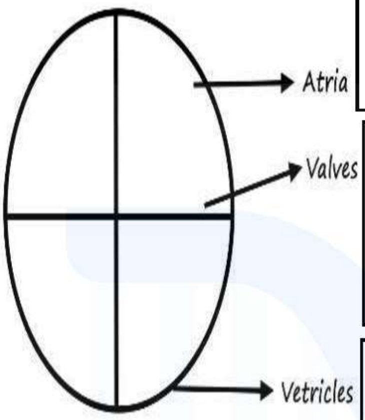


vegetations
infective
IE
Bulky valve chordae pap
Max damage
Max
Non infective
RHD
SLE (libman sacks intense - valvulitis
NBTE
hypercoagulability
mucinous
marantic
≠
2nd mc
virchow
Alf Bf
endothelial injury

DOT TUTORIALS LOGIN FOR SUCCESS

# CARDIAC TUMORS

- M/C Cardiac tumors – Metastasis – commonly from lung
- Site of lodgment of Mets → pericardium
- M/c 1°



Atrial Myxoma

M/c1° tumor of heart in adults

Papillary Fibroelastoma

m/c tumor arising from valves

Rhabdomyoma

M/C 1° Tumor of heart in Children

## Childhood cardiac Tumor 00:02:16

- M/C – Rhabdomyoma
  i. Tumor of skeletal Muscle
  ii. Usually Occurs in Patients of tuberous Sclerosis
  iii. Microscopy – lots of Glycogen filling cytoplasm

**Spider cells**

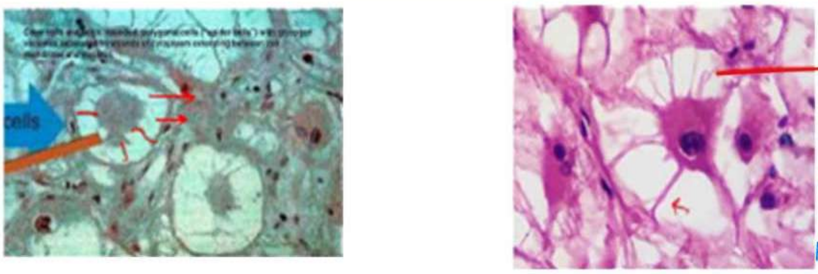


Fig: 1

**Glycogen stained by**

i. PAS

ii. Best Carmine stain

- Gross of Rhabdomyoma -tumor of ventricles

## Papillary Fibroelastoma 00:04:58

- M/C Tumor of valves
- Hong's like a papillary Fronds form valves

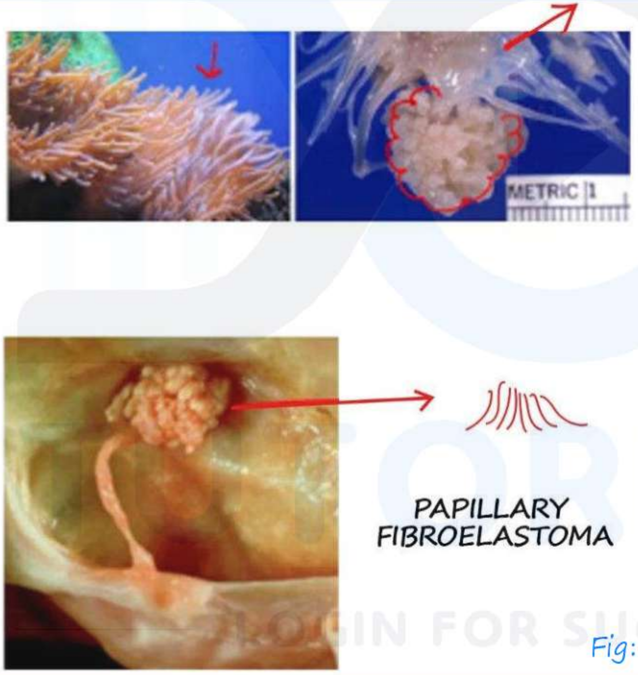


Fig: 2

TORIALS
LOGIN FOR SUCCESS

## Myxoma 00:05:54

MYXOMA

**Associated with**

i. GNAS mutation (or)

ii. PRKAR mutation

**Associated with syndromes**

i. Carney complex

ii. Me cune Albright syndrome

## carney complex

- Triad of

i. Spotty pigmentation

ii. Myxoma

iii. Connective tissue & Endocrine tumors

2 syndromes under CARNEY complex

| NAME Syndrome | LAMB syndrome |
|---|---|
| Nevi | Lentigines |
| Atrial Myxoma | Atrial myxoma |
| Myxoid neurofibroma | Blue nevi |
| Ephelides (freckles) | |

## Remarks:

| Carney Triad | CARNEY STRATARSIS syndrome |
|---|---|
| Sporadic | Familial |
| GIST | GIST |
| Paraganglioma | Paraganglioma |
| Pulmonary chordoma | GIST |
| | SDH delicient GIST |
| GIST occurring are indolent & Resistant Imatints | Site -Antrum |
| | Child & young Females |

- On IHC – Loss of SDH – b & increase IGF -1R in Both types of GIST

## McCune – Albright Syndrome

- Associated with mutation of GNAS gene
- Traid of
  i. Café -au-lait spots
- Also, a/w pituitary tumors and Myxoma

Café au lait spots in

| **Mc Cune Albright Syndrome** | **Neurofibromatosis** |
|---|---|
| •Irregular spots like Coast of Maine | •smooth edged cafe-au<br>•Lait spots like<br>•Coast of California |

COAST OF MAINE-MAS

COAST OF CALIFORNIA

## MYXOMA

- m/c Location – Fossa Ovalis
  LA> RA
- Gross – Myxoid – appearance because it contains Lots of Mucopolysaccharide
- Microscopy, Typical cells → Lepidic cells
- Myxoma causes Ball Valve effects in Atrium
- Release IL – 6 → so can causes Systemic manifestation

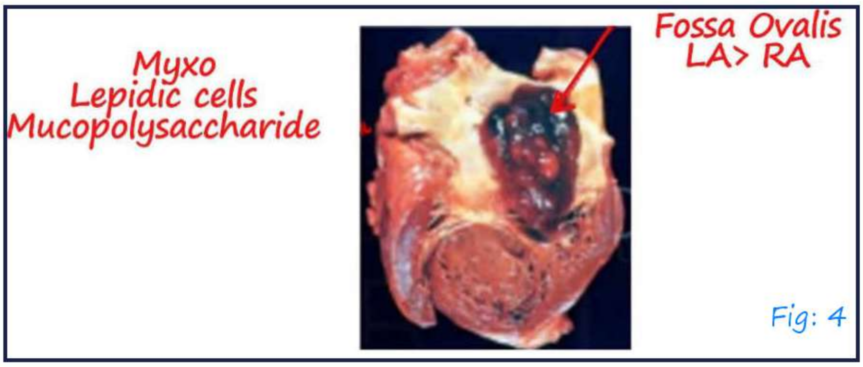

Myxo
Lepidic cells
Mucopolysaccharide
Fossa Ovalis
LA> RA

Fig: 4

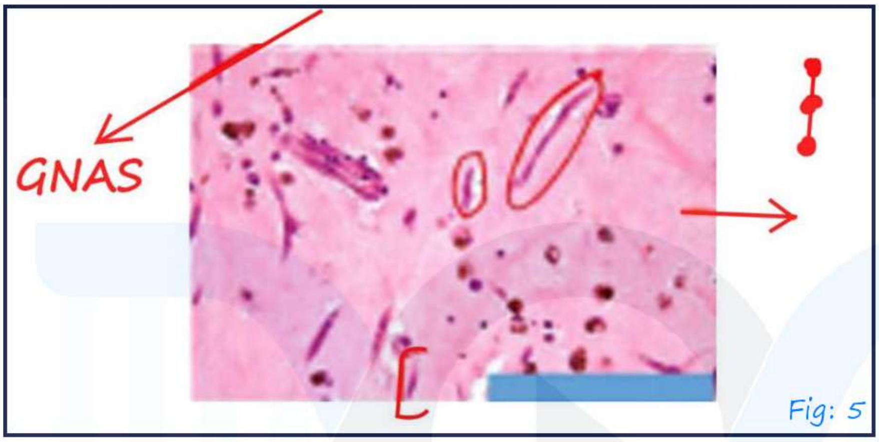


Fig: 5

### Lambl Excrescences

- Wear & tar effect /Aging effect on endocardium
- Closest differential of papillary fibroelastoma

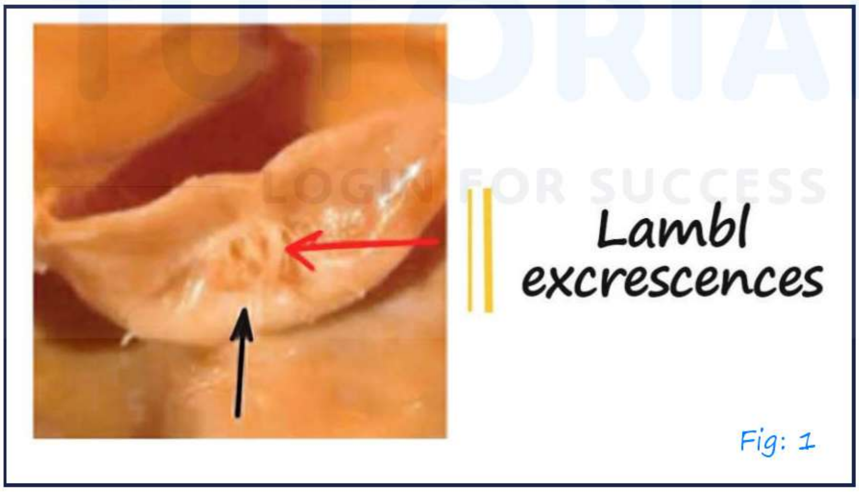

Lambl
excrescences

Fig: 1

# HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (NOCM)

## Hypertrophic Obstructive Cardiomyopathy (NOCM) 00:00:10

↓

Hypertrophy of interventricular septum

- Hyper contracting heart
- Diastolic dysfunction

## Etiology 00:01:30

i. Genetic mutations seen in 100% of cases
  - Defective sarcomere function due to defect in myosin nearby chain – B
  - Usually young people, presents with sudden death

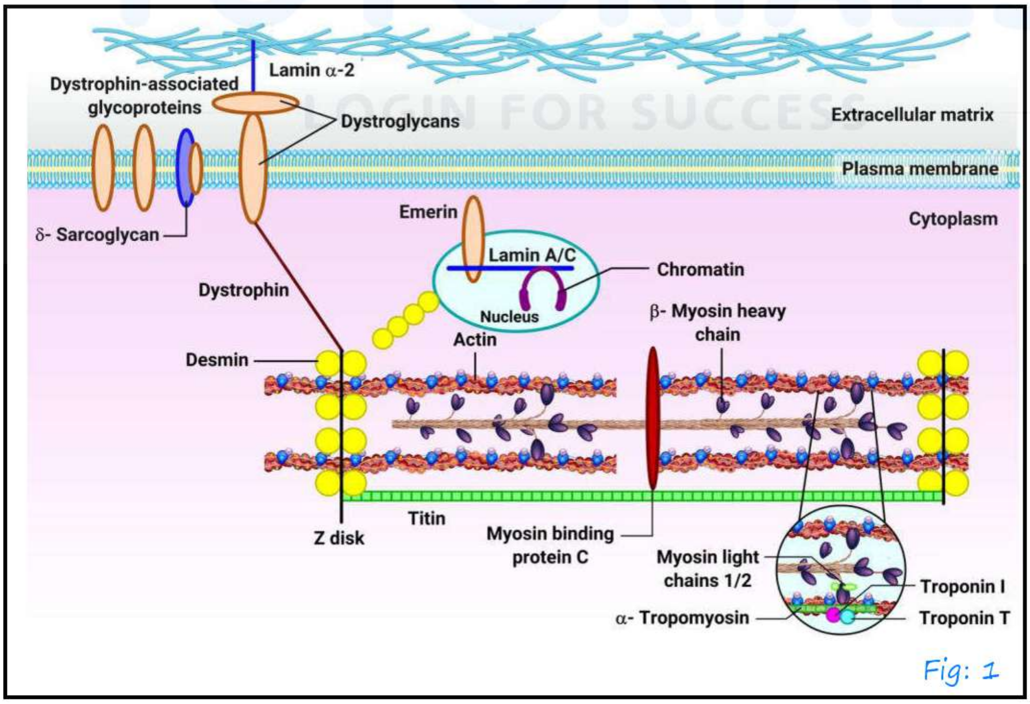

Lamin α-2
Dystrophin-associated glycoproteins
Dystroglycans
Extracellular matrix
Plasma membrane
Cytoplasm
δ- Sarcoglycan
Emerin
Lamin A/C
Chromatin
Nucleus
Dystrophin
β- Myosin heavy chain
Actin
Desmin
Titin
Z disk
Myosin binding protein C
Myosin light chains 1/2
Troponin I
Troponin T
α- Tropomyosin

Fig: 1

- Tropomyosin, Troponin I, Troponin T mutations are also common
- Myosin binding protein C mutation seen in elderly patients of HOCM
  1. Infants of diabetic mother
  2. Patients of Friedrich ataxia

## Pathogenesis 00:06:00

Pathogenesis – Obstructive (HOCM)
Non obstructive (HCM)

- Septa thickens in the sub aortic part
- Septa: LV ratio becomes 3:1 in most cases
- For HOCM septa: LV should be > I:5:1
- Cavity becomes banana shaped

DOC TUTORIALS
LOGIN FOR SUCCESS

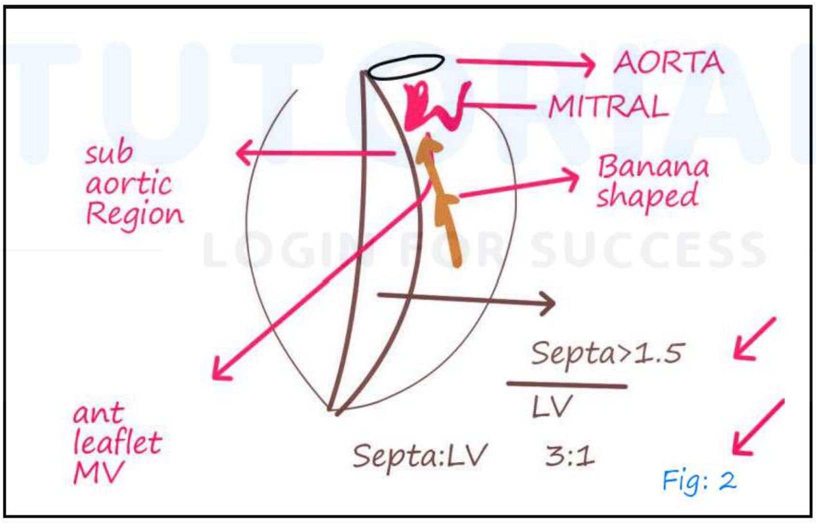

AORTA
MITRAL
sub aortic Region
Banana shaped
Septa>1.5
LV
ant leaflet MV
Septa:LV 3:1

Fig: 2

- Anterior leaflent of mitral value hits the hypertrophied septum obstructing outflow – systolic anterior movement of mitral value is the cause of obstruction in HOCM

Non-obstructive

Fig: 3

- Sudden collapse after rcercise – presentation of NOCM

## Microscopy 00:13:02

1) Thickened myocyte > 40 μm. Normal □ 15 μm

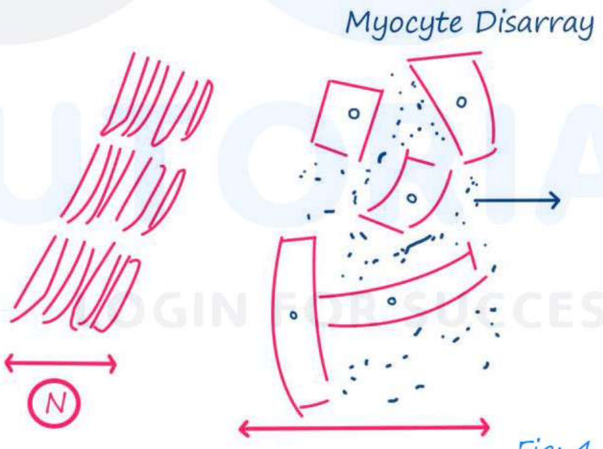

Myocyte Disarray
N

Fig: 4

2) Haphazardly arranged dilated myocyte – myocyte disarray marson
3) Interstitial fibrosis between myocytes – visualized by trichrome stain

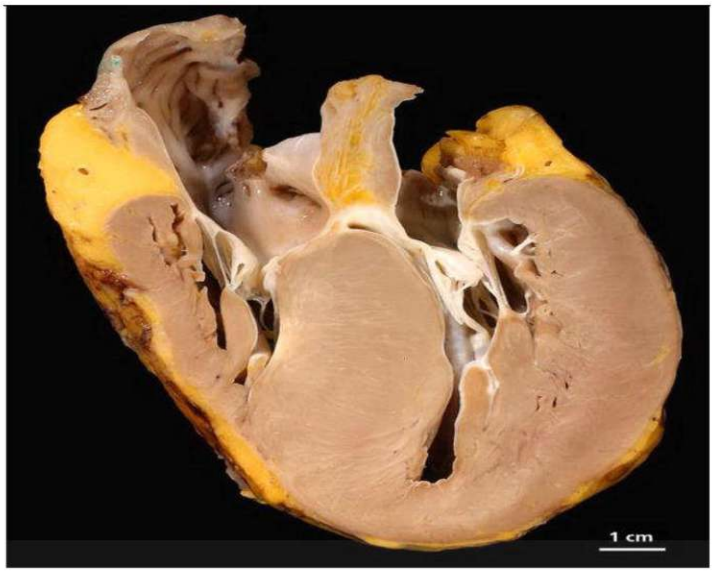


Fig: 5

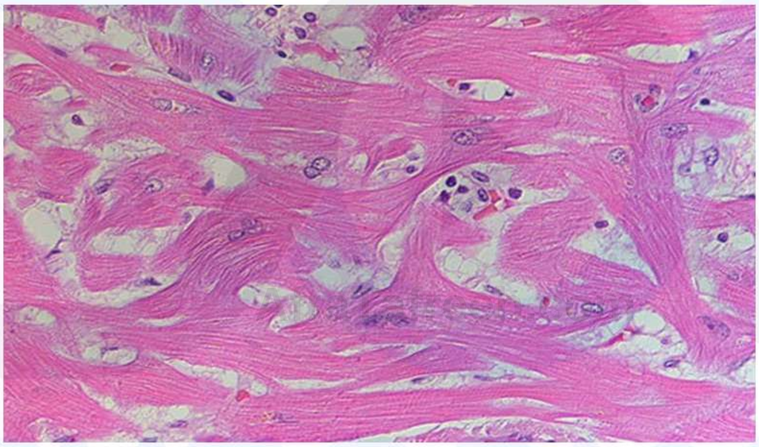


Fig: 6

## Genetic rcanination of MOCM patient: 00:18:50

- Most common mutation in myosin heavy chain and coded by MYN 7 gene
- Myosin binding protein (Mutation – in elderly – better prognosis
- β blockers
- myomectomy – Morrow's – Ablation of IV septal muscle procedure

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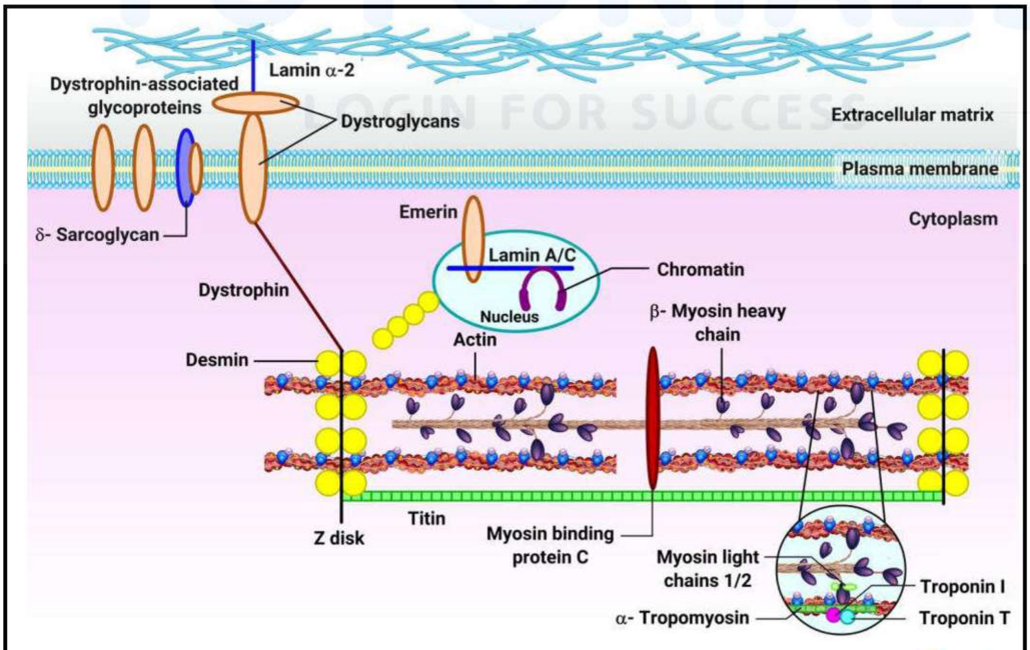
Lamin α-2
Dystrophin-associated glycoproteins
Dystroglycans
Extracellular matrix
Plasma membrane
Cytoplasm
δ- Sarcoglycan
Emerin
Lamin A/C
Chromatin
Dystrophin
Nucleus
β- Myosin heavy chain
Actin
Desmin
Titin
Z disk
Myosin binding protein C
Myosin light chains 1/2
Troponin I
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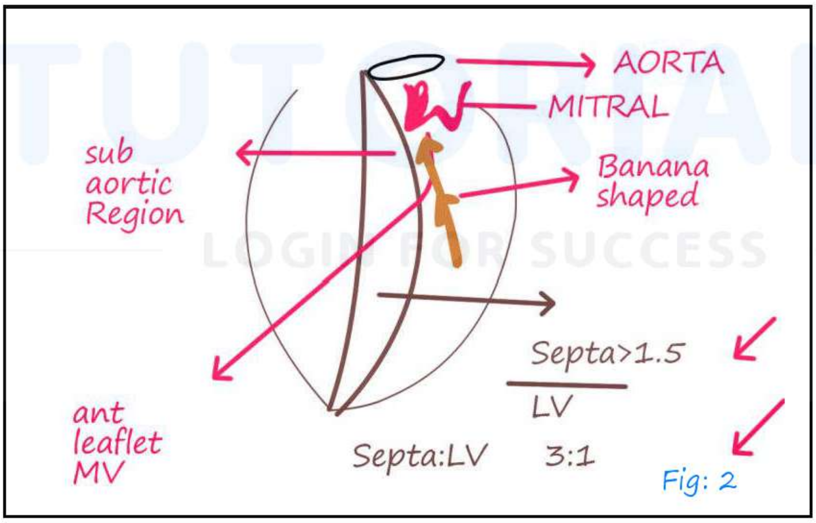
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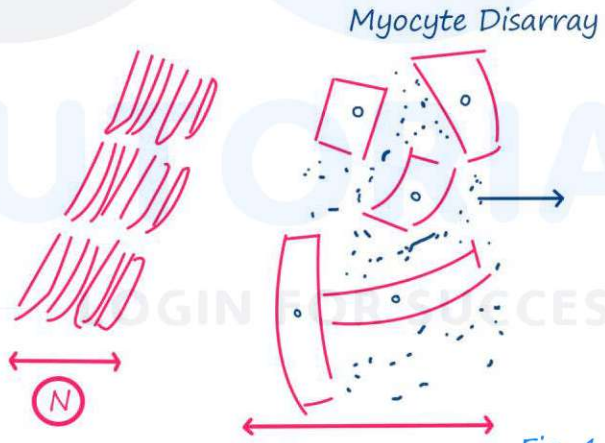
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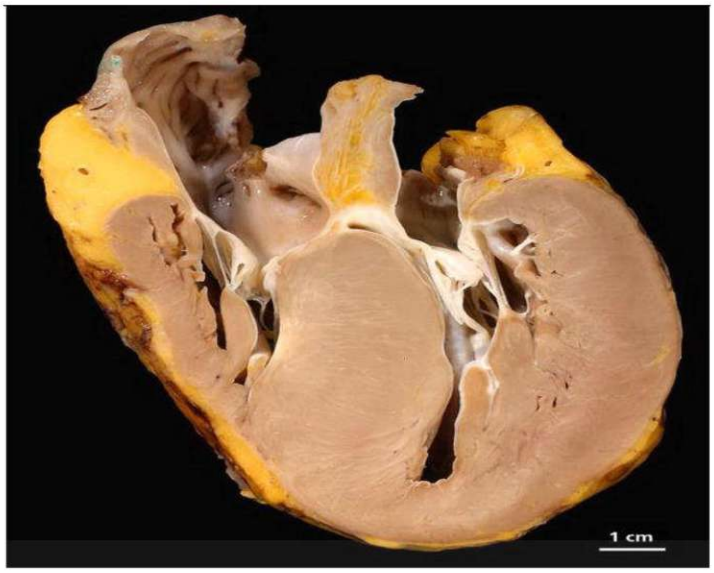
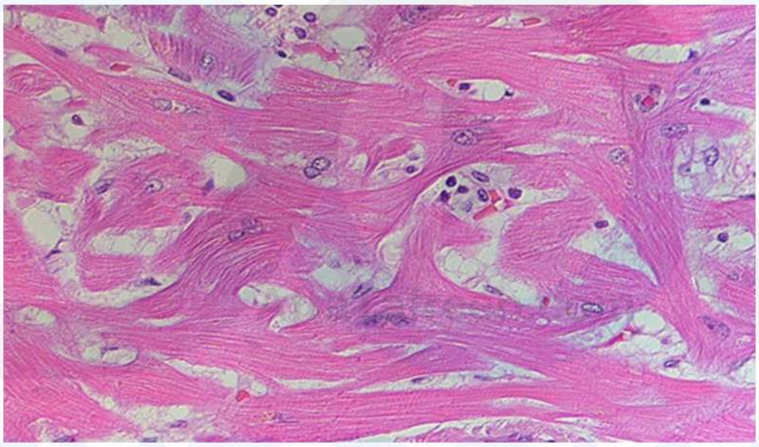


Fig: 5



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- myomectomy – Morrow's – Ablation of IV septal muscle procedure

# DIAGNOSIS OF SYPHILIS

## Diagnosis of syphilis 00:00:07

**Direct Demonstration**

- Dark field microscopy
- Special stains
  ↓
  Sliver stains
  i. Masson Fontana
  ii. Steiner satin
  iii. Warthin starry

**Serological methods**

Non –specific
↓
Non –Treponemal test

Specific
↓
Treponemal test

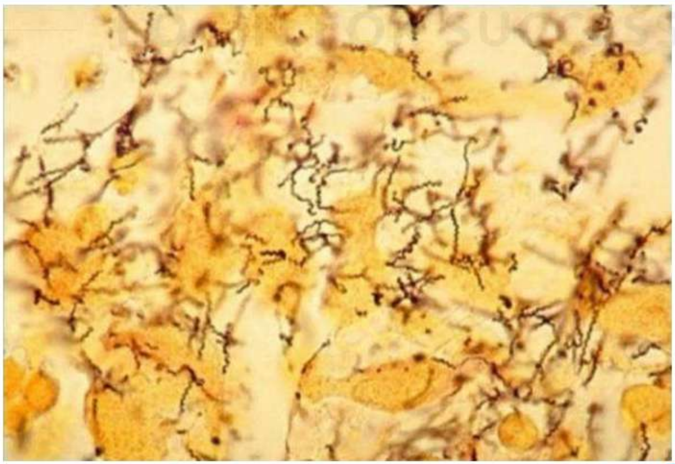


Fig 1

| Nonspecific test | Specific test/treponemal test |
|---|---|
| • Defects IgG or IgM against Cardiolipin antigen<br>i. Rapid Plasma Reagin (RPR)<br>• Test of choice for Rapid Diagnosis<br>ii. DRL-Venereal Disease Research Laboratory<br>• Test of choice for Response to therapy & for examining CSF<br>• Become negative after Treatment<br>• RPR or VDRL are done by EIA –Elisa Immune assay<br>• Non-specific tests are done in screening of Blood before Blood transfusion. | • Detects specific antibody against T-pallidum<br>• Don't become negative after therapy. so not used for follow up or monitoring of treatment<br>• Includes<br>i. Fluorescent treponemal antibody absorption test FTA –Abs<br>ii. Treponema pallidum particle agglutination – TPPA |

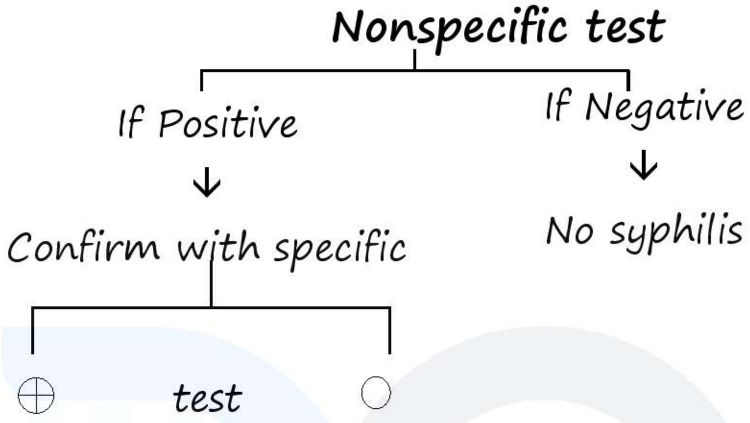
- FTA –Abs, TPPA are most sensitive test.
- TPI is most specific serological test.

AiraTafreeh.com

TUTORIALS LOGIN FOR SUCCESS

- TPPA has supplanted FTA-Abs as diagnostic test

## Protocol for Diagnosis of Syphilis 00:09:14


**Nonspecific test**
If Positive
Confirm with specific
⊕
test
○
If Negative
No syphilis

## Diagnosis of congenital syphilis 00:10:19

1. Both VDRL and FTA- Abs – IgM positive (specific) positive in infant
2. Antibody Titer in infant 4 times that in mother
   E.g.: mother 1:16 4X
   Infant 1:64
3. Examination of CSF, eyes, teeth and ear.

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# SYPHILIS

## SYPHILIS 00:00:06

- Caused by a spirochete –Treponema palladium
- Spreads Via

i. Sexual Route

ii. Transfusion

iii. Mother to child

↙ ↘

In utero or During Birth

### Treponema palladium

- Gram –ve Bacteria

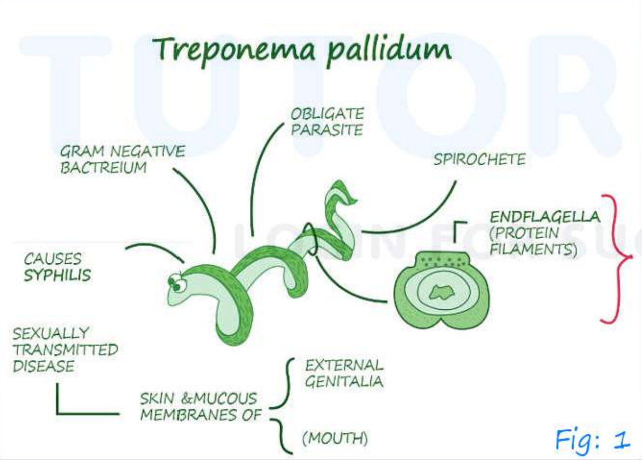

Treponema pallidum
OBLIGATE PARASITE
GRAM NEGATIVE BACTREIUM
SPIROCHETE
ENDFLAGELLA (PROTEIN FILAMENTS)
CAUSES SYPHILIS
SEXUALLY TRANSMITTED DISEASE
SKIN &MUCOUS MEMBRANES OF
EXTERNAL GENITALIA
(MOUTH)

Fig: 1

- This spiral organism actively motile through endoflagella
- Obligate parasite

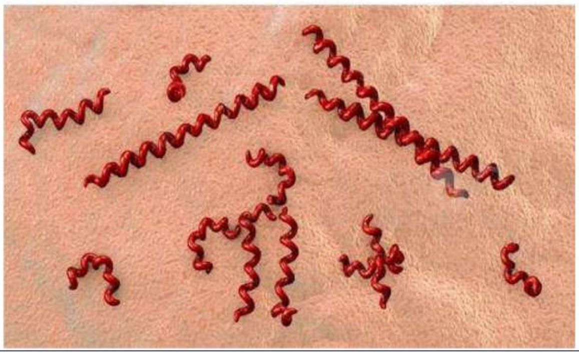
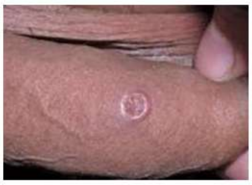
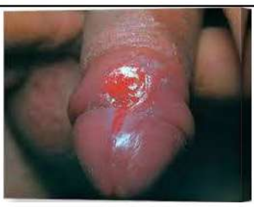
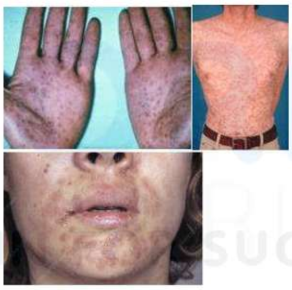
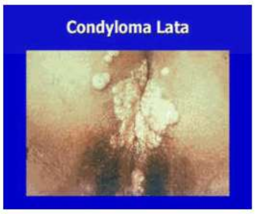


Fig: 2

## Clinical Presentation of Syphilis

| Primary syphilis | Secondary syphilis | Tertiary syphilis |
|---|---|---|
| i.Chancre - Painless, indurated non-bleeding usually single punched out ulcer with rolled edges at the site of entry of spirochete<br>ii. Occurs 1-3 week after exposure<br>• Heals within 4-6 Weeks (even without treatment<br> | i. B/L symmetrical asymptomatic localized or diffuse muco-cutaneous lesion (macule, papule, papulosquamous and rarely pusture)<br>- Typically, in palms soles, oral cavity<br>ii. non-tender generalized lymphadenopathy<br>iii. Highly infectious | Gummas CNS CVS<br>Granulomatous lesion<br>CNS-Neurosyphilis, Tabes Dorsalis<br>CVS-Aortitis, Aortic insufficiency, Coronary stenosis and nocturnal angina Ostitis, periostitis. |

| | | |
|---|---|---|
| <br>iii. Location chancre: Heterosexual male-penis female –Cervix, Labia<br>iv.In syphilis transmitted by Blood transfusion chancre does occur.<br>v. Painless Rubbery, shotty Lymphadenopathy | Condyloma lata – painless lesion in warm moist intertriginous areas. Especially scrotum & vulva.<br>iv. Moth eaten alopecia arthritis, proteinuria<br>2° syphilis occurs 6-12wks after exposure.<br><br><br> | |

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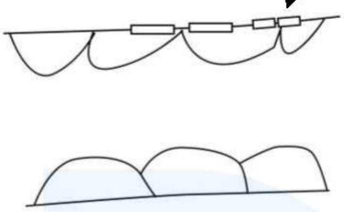
## Clinical progression of syphilis:

**1° Syphilis**

Chancre

↓

Treponema enters in blood stream



↓

lymphadenopathy

Inflammation of endothelial cells

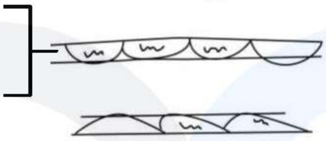
↓

Rashes condyloma lata + Lymphadenopathy

**2° Syphilis**

↓

Latent syphilis



Treponema stays in endothelium

| ↓ | ↓ |
|---|---|
| B cells | APC activated |
| ↓ | ↓ |
| Plasma cells | Ag + APC |
| ↓ | ↓ |
| Anti body | T cells |

↓

TH1

↓

IFNγ

↓

Macrophages → Epitheloid cells

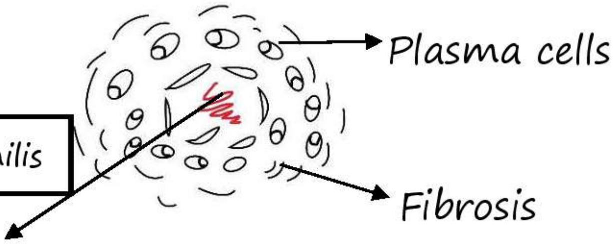
↓

Granuloma

↓

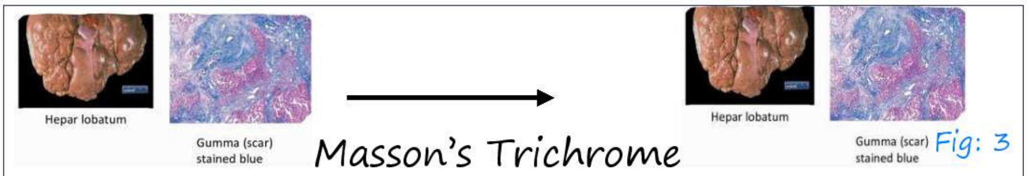
**Gumma**

**Tertiary syphilis**



Coagulative Necrosis

- Gumma formation takes 10 or more years develop and affects skin subcutaneous tissues, mucus membranes submucosa liver, Spleen and Bones.

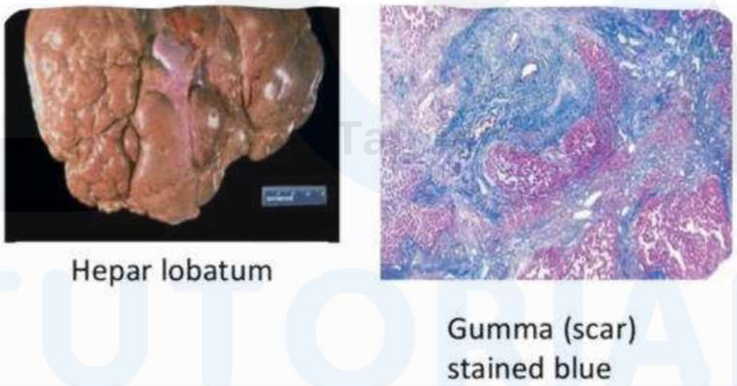

Hepar lobatum
Gumma (scar) stained blue
Hepar lobatum
Gumma (scar) stained blue

Masson's Trichrome

Fig: 3

## Hepar lobatum

- Irregularly contracted liver with dense band of Fibrosis


Hepar lobatum
Gumma (scar)
stained blue

Gumma in skin

Fig: 4

## Pathogenesis of CVS manifestations of tertiary syphilis 00:17:31

- Fibrosis of Vaso Vasorum of vessels → Narrowed vaso-vasorum

(Small blood Vessels that Supply walls of large B.V Such as elastic arteries Eg: Aorta)

↓

Intimal fibrosis of large B.V eg: Aorta

↓

Tree bark appearance of Aorta

↓

Weakened vessel wall

↓

Ascending Aortic aneurysms, Thoracic aorta Aneurysm

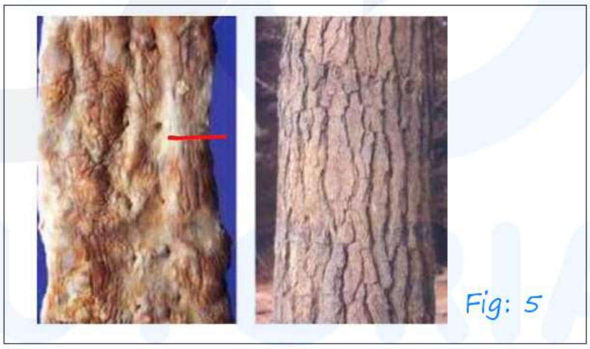


Fig: 5

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## Neuro – syphilis 00:20:15

a. 5 presentations

- i. Asymptomatic
- ii. subacute Meningitis
- iii. Meningo vascular syphilis
- iv. Tabes Dorsalis (Involvement of posterior Column of spinal cord)

↓

Loss of vibration & position seen

v. General paresis of Insane

b. Argyll Robertson pupil (ARP)

- Accommodation Reflex present
- light Reflex lost.

## General paresis of Insane

- Progressive disease – nerve cells – brain – mental deterioration – psychiatric symptoms
- Psychiatric symptoms like Delusion of Grandeur
- Pneumonic –PARESIS

P-**P**ersonality changes

A-Alteration of **A**ffect

R-Hyperactive **R**eflexes

E-**E**ye→ARP

S-changes in **S**ensorium

I-Decreased **I**ntellect

S-Slurred **S**peech

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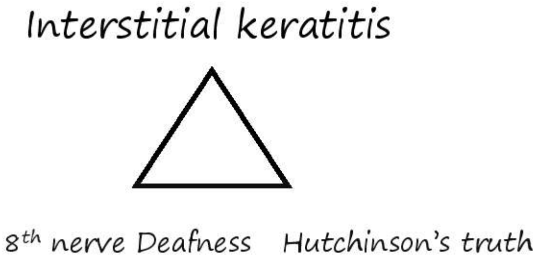
## Congenital syphilis 00:25:49

| Still Birth | Early congenital Syphilis | Late congenital Syphilis |
|---|---|---|
| | i. Snuffles (Rhinitis) in earliest feature<br>ii. Snail track ulcers in Mucosa<br>iii. Lesions are vesicobullous<br>iv. Osteochondritis, periostities<br>v. Liver & lung fibrosis | i.Hutchinson's Triad<br> Interstitial keratitis<br>8th nerve Deafness<br>Hutchinson's truth<br>ii. Saddle nose, sabre Tibia, mulberry molars<br>iii. Rhagades (Linear scar at angle of moth noses)<br>iv.Clutton's joint (painless swelling of joints, M/C both knee)<br>v. Palatal perforation<br>vi.higoumenakis sign (Periostitis leading to U/L enlargement of sterna end of clavicles) |

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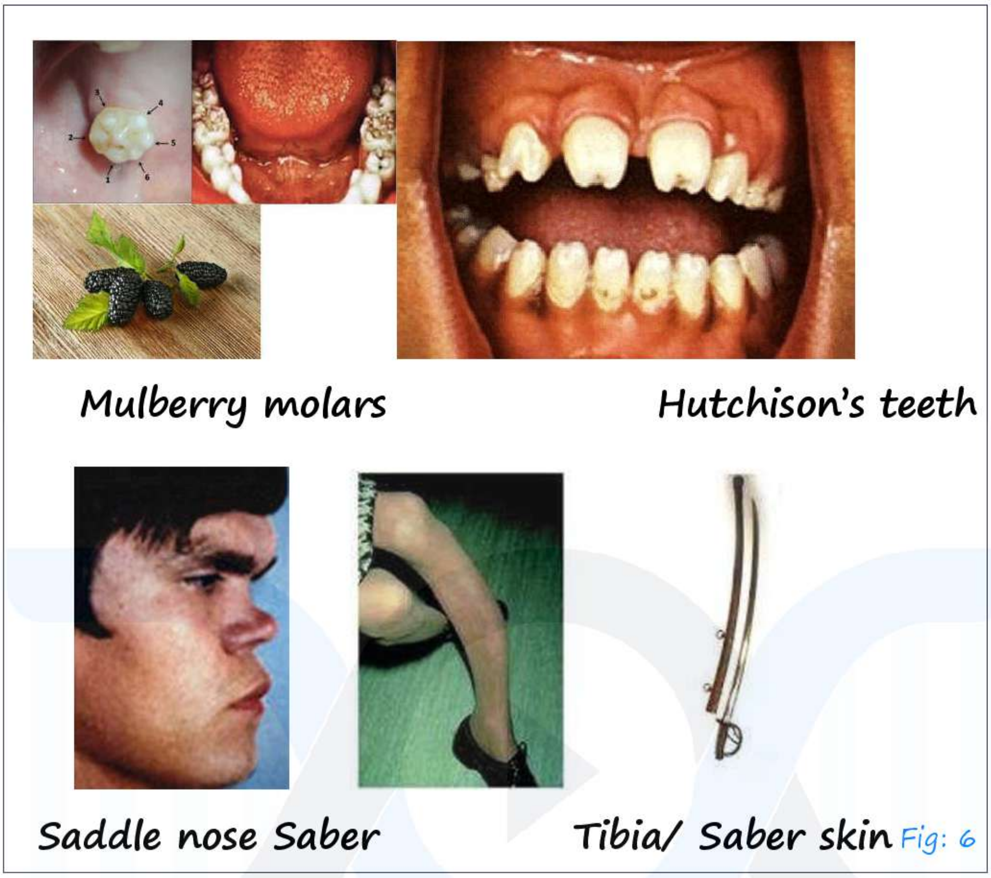
## Pegged central Upper Incisors


Mulberry molars

Hutchison's teeth

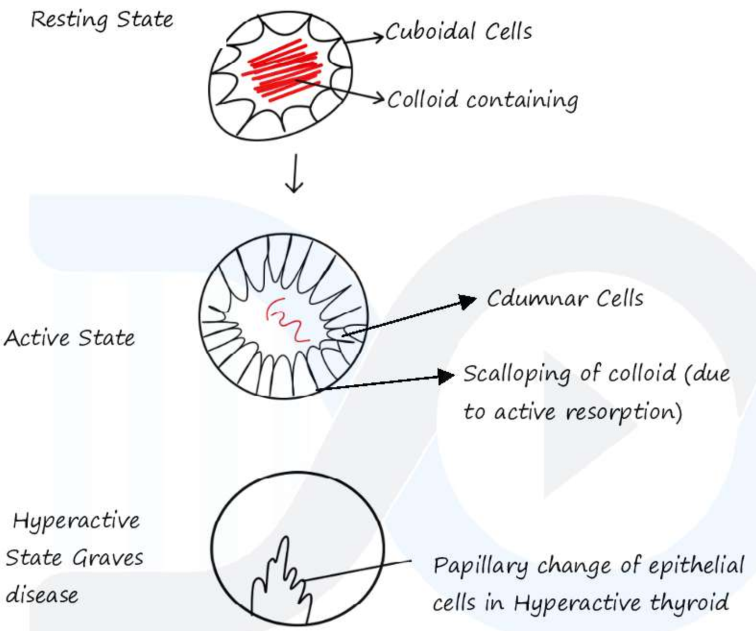
Saddle nose Saber

Tibia/ Saber skin Fig: 6

# BASICS OF THYROID – GRAVES & THYROIDITIS

## Thyroid follicles

### Basics 00:00:40


Resting State
Cuboidal Cells
Colloid containing
Active State
Cdumnar Cells
Scalloping of colloid (due to active resorption)
Hyperactive State Graves disease
Papillary change of epithelial cells in Hyperactive thyroid

Resting State

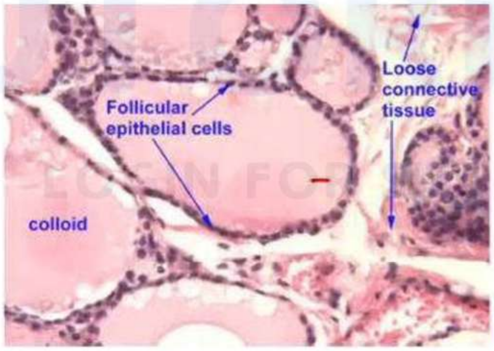

Follicular epithelial cells
Loose connective tissue
colloid

Fig: 1

Active State

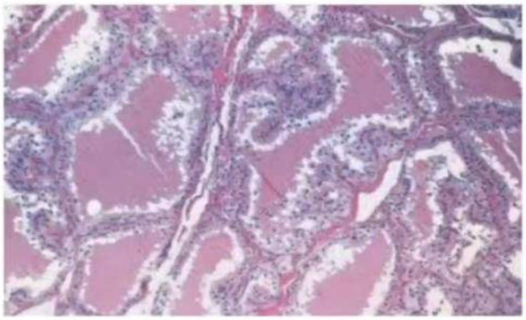


Fig: 2

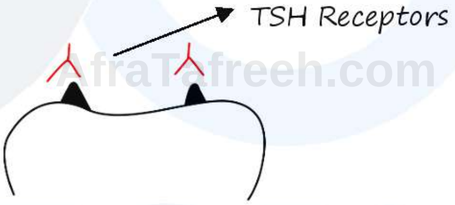
- On cut section normal thyroid gland appears Tan colored

## Grave's Disease 00:04:55

### **Grave's Disease / Basedow Disease**

- Pathogenesis

Antigen (Alternation of CTLA4 or MHC2)
CD4 T cell
↓ ⊕
Plasma cells
↓
Anti – TSH receptor antibodies
↓
Thyroid stimulating Immunoglobulins – IgG
↓



↓
increase CAMP
↓
increase Thyroid hormone secretion
↓
Hyperthyroidism

- Grave's Disease shows alternation in HLA – B8 & HLA – DR3 (m/C alteration on MHC – II)
- Update – New polymorphic gene called Major histocompatibility complex close I chain – related gene A
- ( MICA) regarded as a risk factor for graves

- MICA – A5 – Increases risk of graves
- MICA A6/ A9 – Prevents graves
- Cut section of thyroid in graves shows beefy red appearance due to consumption of colloid in the hyperactive thyroid gland

### On FNAC

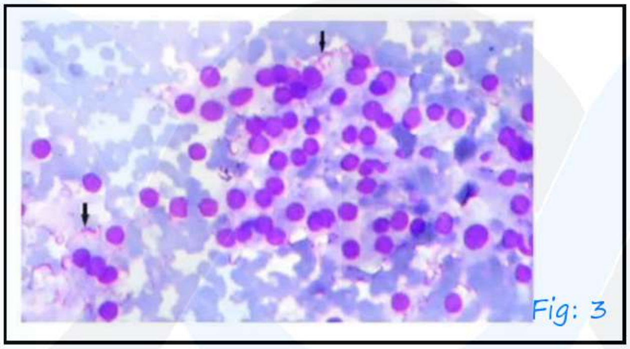
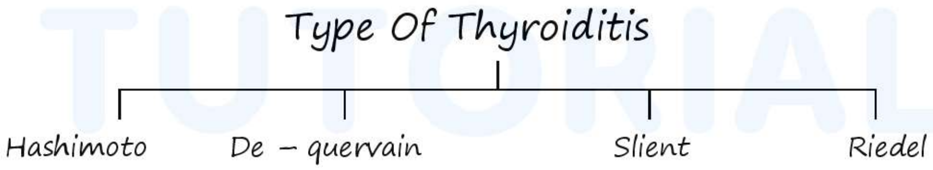


Fig: 3

- Fire flares (Dilated Endoplasmic reticulum)


Type Of Thyroiditis
Hashimoto
De – quervain
Slient
Riedel

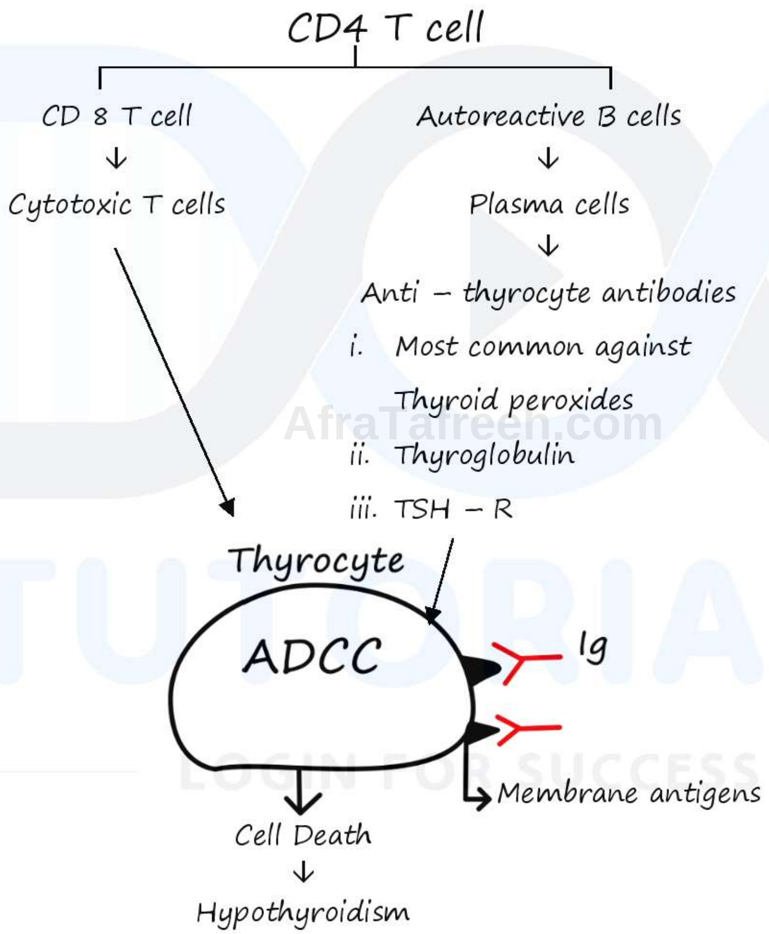
## Hashimoto's Thyroiditis 00:15:36

### I. Hashimoto's Thyroiditis

- Microscopy:- Lymphoid follicles, atrophied thyroid follicles and hurthle cells
- Antibodies against TPO
- M/C lC of Thyroiditis / hyperthyroidism (Struma lymphomatosa )

- Autoimmune Thyroiditis , common in women
- Initially Patients present with Toxic features but manifest with feature of Hypothyroidism
- Can give rise to Papillary carcinoma of thyroid or MALTOMA

## Pathogenesis


CD4 T cell
CD 8 T cell
Cytotoxic T cells
Autoreactive B cells
Plasma cells
Anti – thyrocyte antibodies
i. Most common against Thyroid peroxides
ii. Thyroglobulin
iii. TSH – R
Thyrocyte
ADCC
Ig
Membrane antigens
Cell Death
Hypothyroidism

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# Adaptation in Thyrocytes

- Cellular Atrophy
- Hurthle cell

↓ Granular pink cells due to lot of Mitochondria

- Lymphocyte infiltration

↓ Formation of Lymphoid follicles

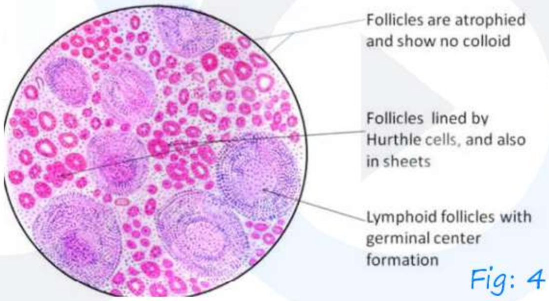

Follicles are atrophied and show no colloid
Follicles lined by Hurthle cells, and also in sheets
Lymphoid follicles with germinal center formation

Fig: 4

Lymphoid follicles

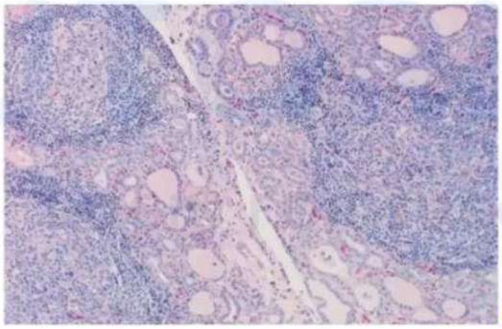


Fig: 5

Hurtle cells or askanzy cells

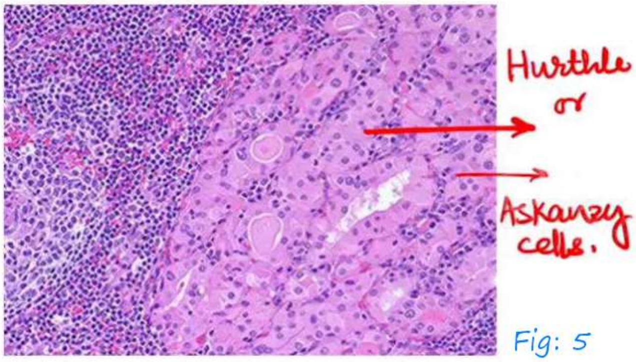
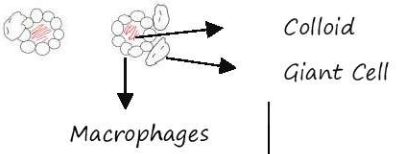
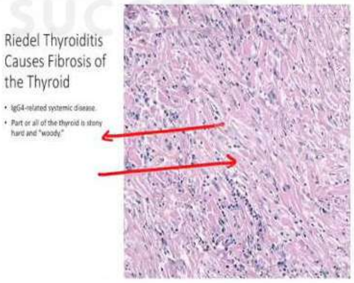

Hurthle or
Askanzy cells.

Fig: 5

| De- quervain's | Silent Thyroiditis | Riedel Thyroiditis |
|---|---|---|
| Subacute thyroiditis, granulomatous thyroiditis or Giant cell thyroiditis | Post partum thyroiditis | Thyroid times is replaced by fibrous times |
| Post viral thyroiditis | Painless Thyroiditis Therefore aka silent thyroiditis | Stony hard / woody thyroid |
| URTI findings - sore throat ear ache , fever | Transient Hyperthyroidism<br>↓<br>Followed by Hypothyroidism<br>↓<br>Majority Recover only 20% have life long Hypothyroidism | Often associated with multifocal fibrosing syndrome<br>• Retro peritoneal fibrosis<br>• Palmar fibrosis duputryen contractures<br>• Ureteric fibrosis<br>↓<br>Ormond's disease<br>• Penile fibrosis peronei's disease<br>• Mediastinal fibrosis<br>• Now considered a part of IgG4 related disease |
| Pain & Tenderness in thyroid | On Microscopy<br>• Lymphoid follicles<br>• But No hurthle cells | |
| On Microcopy<br> | | <br>Riedel Thyroiditis Causes Fibrosis of the Thyroid<br>• IgG4-related systemic disease.<br>• Part or all of the thyroid is stony hard and "woody." |
| Granuloma Formation Giant Cells | | |
| Vavally a self limiting disease | | |

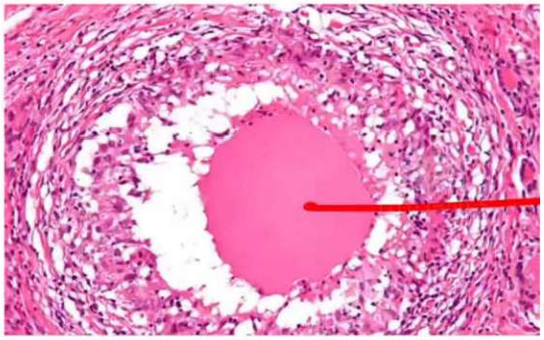


Fig: 6

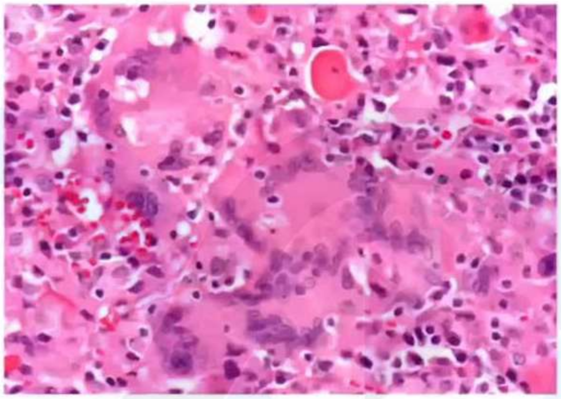


Fig: 7

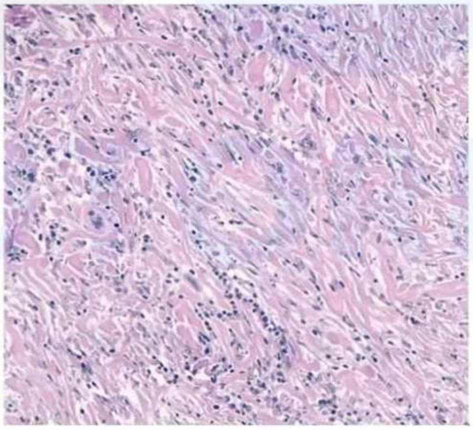


Fig: 8

# MALIGNANCIES OF THYROID

## Types 00:00:15

**Benign**

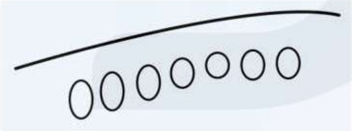
**Follicular adenoma**

Well defined encapsulated tumor nodule

**Malignant (Dunhill classification)**

i. Papillary carcinoma
ii. Follicular carcinoma
iii. Medullary carcinoma
iv. Anaplastic carcinoma

### Microscopically



→ Micro follicular

→ Trabecular

→ Hurtle cell (abundant pink cytoplasm

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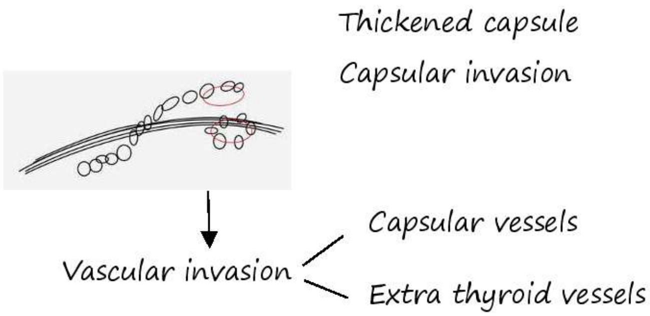
### Hurthle cell adenoma

- Adenoma shows hurtle cell change
- RAS mutation: Most common mutation in non – functional follicular adenoma, no capsular or vascular invasion

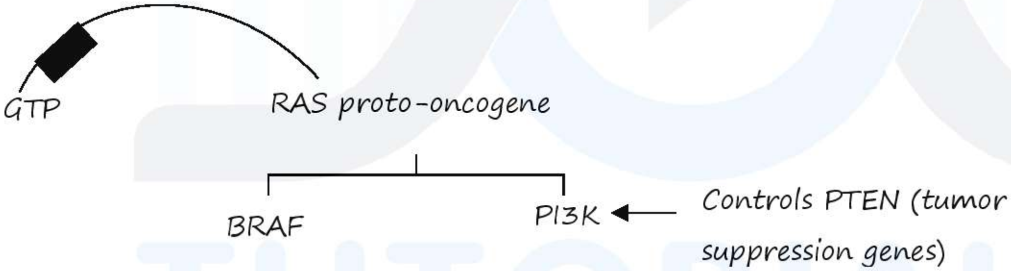
## Follicular carcinoma 00:04:16


Thickened capsule
Capsular invasion
Vascular invasion
Capsular vessels
Extra thyroid vessels

## Molecular pathogenesis of follicular carcinoma

00:06:13

- Normal proliferation epithelial cells is dependent on GTP pathway


GTP
RAS proto-oncogene
BRAF
PI3K
Controls PTEN (tumor suppression genes)

**Alteration of this pathway is involved in follicular ca**

**Mutation**

- RAS mutation – M/C
- PI3 kinase mutation
- Cowden syndrome – mutation of PTEN

**Toxic adenoma**

- Not associated with RAS mutation

- There is mutation of alpha unit of G protein, gene is GNAS
- So toxic adenomas have GNAS mutation on chromosome 20q
- Also common is TSH-R mutation

**Gist: -**

- Toxic follicular adenoma: GNAS (20q)

  TSH-R
- Non – functional adenoma: RAS

  PI3K

  Cowden syndrome
- Areas with iodine deficiency -> high chance of multinodular goiter

↓

Toxic adenoma

↓

Follicular carcinoma

- So follicular carcinoma is M/C thyroid malignancy in iodine – deficient areas
- Metastasis is through vascular dissemination
- Bone secondaries are typically, vascular, warm, pulsate, commonly in skull, long bone

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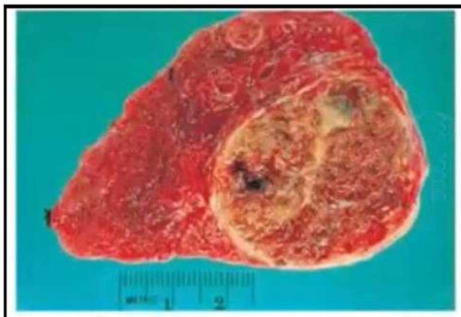


Fig: 1

| **Follicular adenoid** | **Adenomatoid nodule** |
|---|---|
| Well defined capsule | Active nodule of multi-nodular gastro lacks capsule |

## Update

- PAX-8:
- Positive in high grade serous of ovary
- Helps in maturation of kidney & thyroid
- PAX-8-PPAR-G mutation -> seen in 10% of follicular carcinoma

# PAPILLARY CARCINOMA

- 70-80% Common
- Female & Younger age group

## Etiology: -

- Most important Risk factor is Radiation Exposure in children
- Arises from follicular epithelial cell.

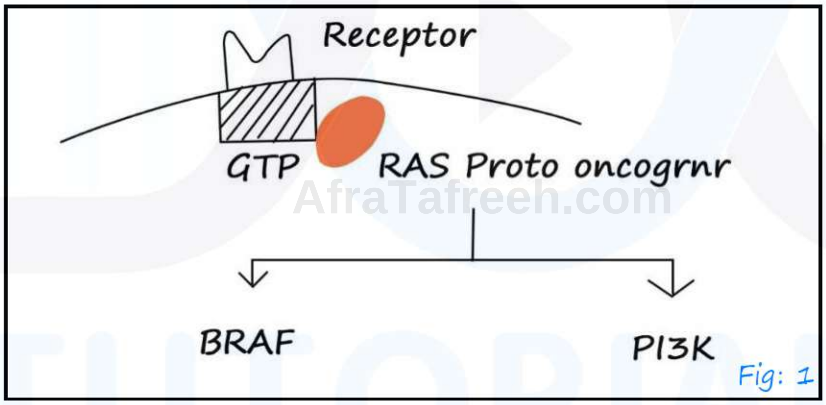

Receptor
GTP
RAS Proto oncogrnr
BRAF
PI3K

Fig: 1

## BRAF Mutation:

- M/C Mutation in Papillary Carcinoma
  - Receptor Mutation
    - RET/PTC Rearrangement
    - Neurotrophic Receptor Tyrosine Kinase mutation (NTRK)
  - BRAF > RET/ PTC > NTRK

## On FNAC:

- Spreads through lymphatics

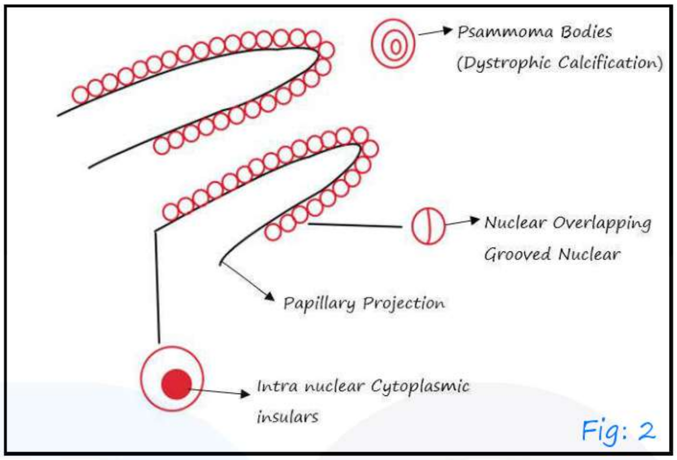

Psammoma Bodies
(Dystrophic Calcification)
Nuclear Overlapping
Grooved Nuclear
Papillary Projection
Intra nuclear Cytoplasmic
insulars

Fig: 2

- Intra Nuclear Cytoplasmic Inclusion.

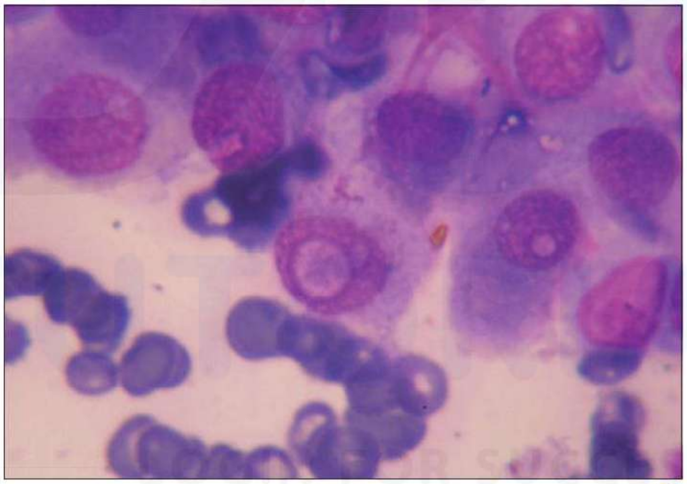


Fig: 3

## On Biopsy:

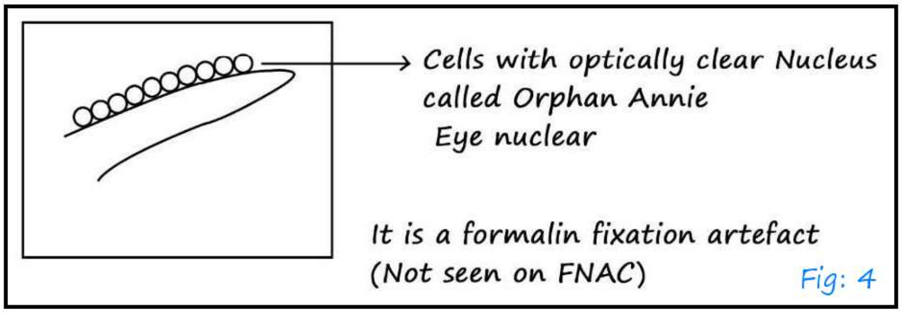

Cells with optically clear Nucleus
called Orphan Annie
Eye nuclear
It is a formalin fixation artefact
(Not seen on FNAC)

Fig: 4

It is a formalin fixation artefact (Not seen on FNAC)

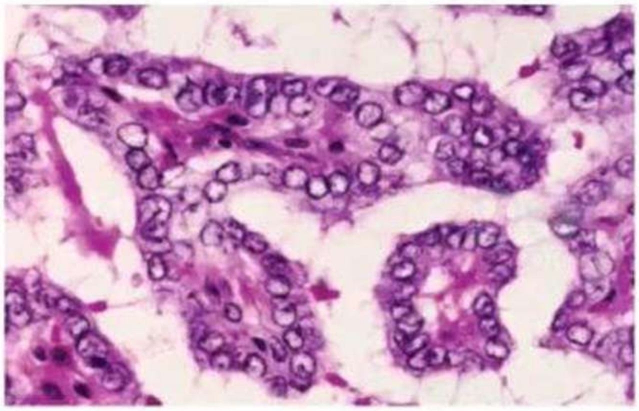


Fig: 5

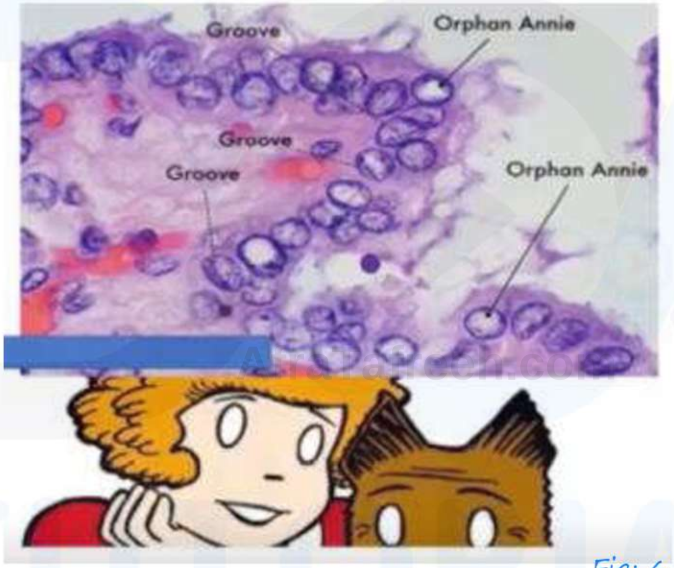

Groove
Orphan Annie
Groove
Groove
Orphan Annie

Fig: 6

**Tumors with Grooves**

i. Langerhans cell Histiocytosis

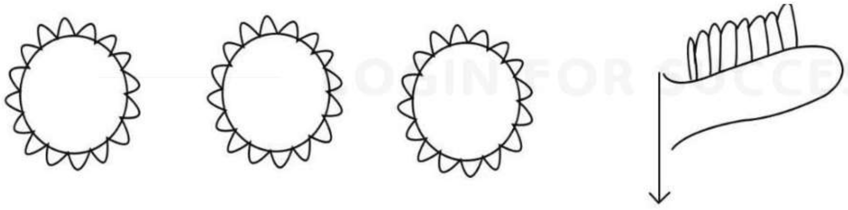
ii. Granuloma cell Tumor of Ovary

iii. Papillary Carcinoma of Thyroid

- **Remember** – Nuclear Features are Diagnostic for Papillary Carcinoma Thyroid
- PCT Is a slowly progressing & less aggrieve Tumor.
- Spreads through lymphatics.

## Variants of Papillary Thyroid Cancer 00:14:57

| Follicular Variant | Tall cell variant | Diffuse sclerosing |
|---|---|---|
| - Tumor cells arranged as follicles but, Nuclear Features resemble Pct. | • Seen in elderly<br>- length of cells linning papillary is 3 times that of width<br>- >30% tumor shows this pattern<br>- BRAF mutation<br>• Poor prognosis | • Occurs in children & yound adults<br>• On histology resembles hashimoto's thyroiditis, with<br>a. Lots of lymphocytic infiltration<br>b. Squamous metaplastic resembling Hurth's cells<br>• No Braff mutation<br>• Have RET/PTC translocation |



- No Braff Mutation
- Have RET/PTC Translocation

Fig: 7

DOC TUTORIALS LOGIN FOR SUCCESS

### Lindsay Tumor

- Length of dells tinning Papillar is 3 times that of width
  - Encapsulated follicular cariant of Papillary Carcinoma
  - Excellent progress
- 30% tumor shows this pattern
- BRAF Mutation

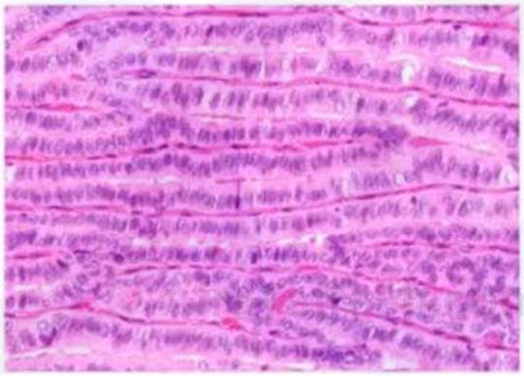


Fig: 8

## Anaplastic Carcinoma 00:20:33

- Arises from follicular Epithetical cells
- An undifferentiated very aggressive Carcinoma
- Occurring in elderly females
- On FNAC Bizarre Giant cells
  Spindle shaped cells mixed.Mixed.
- Very High Mitotic activity
- Poor Prognosis

TUTORIALS LOGIN FOR SUCCESS

**Mutation:**

- RAS
- PI3K
- p53

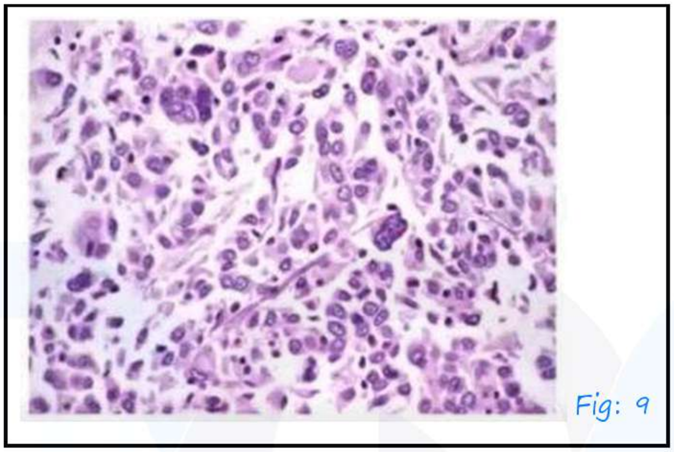


Fig: 9

## Medullary Carcinoma Thyroid 00:23:17

- Does not arise from follicular cells
- Origin – Para follicular ' C ' Cell
- Precursor lesion –'C' cell Hyperplasia
- On Histology – Shows single dispersed Plasmacytoid cells with Nucleus towards one end

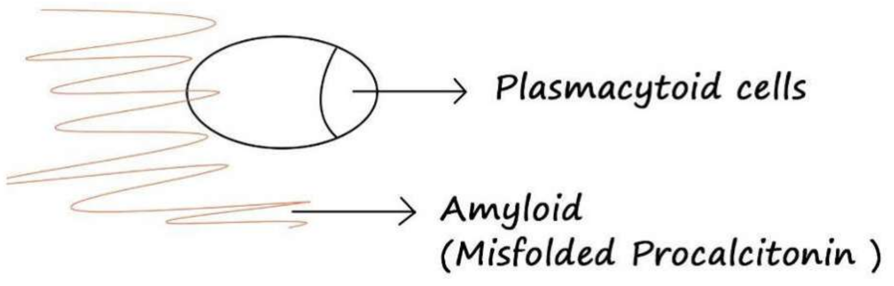
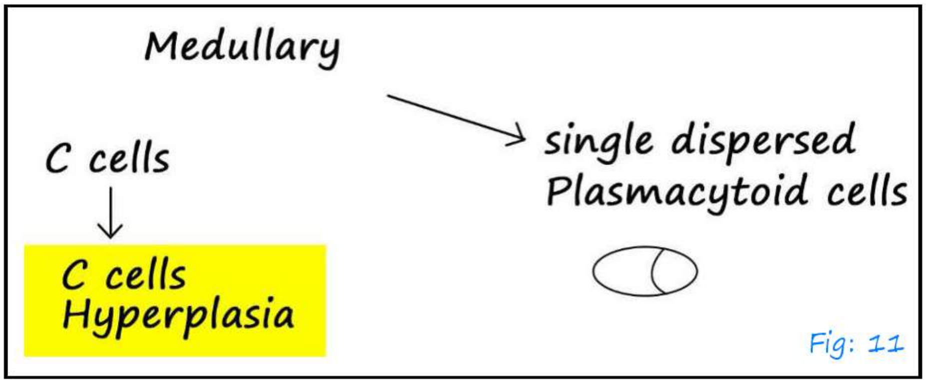

Plasmacytoid cells
Amyloid
(Misfolded Procalcitonin )

Fig: 10



Medullary

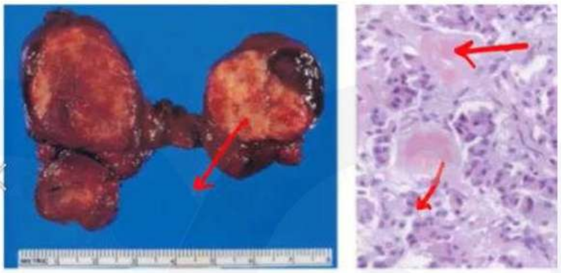
C cells

↓

C cells Hyperplasia

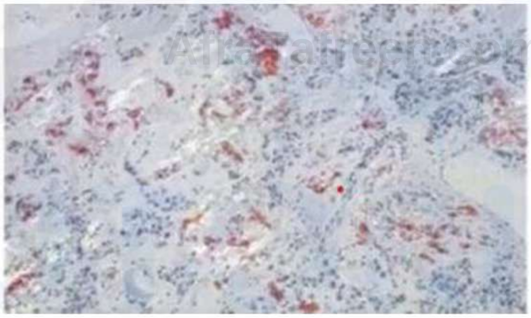
→ single dispersed Plasmacytoid cells

Fig: 11



Grey white Tumor

Fig: 12



Congo Red Positivity

Fig: 13

Types

Sporadic
- Shows RET Point muations

Familial
- Associated with men
  – 2 syndromes
- RET oncogene activation

Papillary Carcinoma

# PITUITARY

## Basics 00:00:42

### Basics of Pituitary

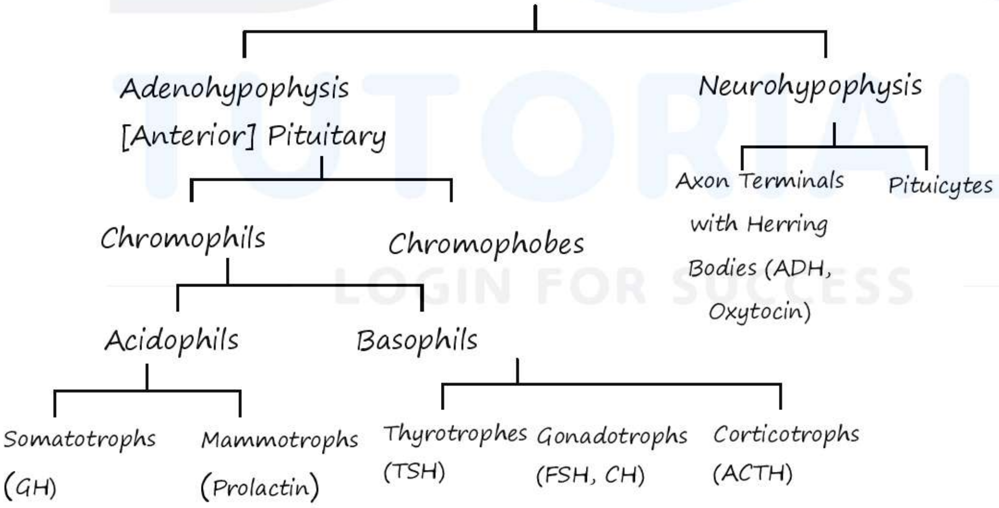
i. Posterior Pituitary

- Arises from Hypothalamus
- Herring Bodies
- Axon terminals derived from Hypothalamus
- It contains ADH and Oxytocin

ii. Anterior Pituitary

- Part of Pituitary – Hypothalamus Portal System

**Pituitary Gland Cells**


Adenohypophysis
[Anterior] Pituitary
Neurohypophysis
Chromophils
Chromophobes
Axon Terminals with Herring Bodies (ADH, Oxytocin)
Pituicytes
Acidophils
Basophils
Somatotrophs (GH)
Mammotrophs (Prolactin)
Thyrotrophes (TSH)
Gonadotrophs (FSH, CH)
Corticotrophs (ACTH)

## Hypopituitary 00:04:56

**Hypopituitary** - Poor Pituitary Function

**Causes**

i. Sheehan's Syndrome
  - (Ischemic) Neurosis of Pituitary due to Hemorrhage commonly due to Post-Partum Hemorrhage

ii. Radiation

iii. Empty Sella Syndrome

iv. Pick hart Syndrome
  - Due to mutation of HES X1 gene
  - Affects Portal System of Pituitary

**Empty sella syndrome**

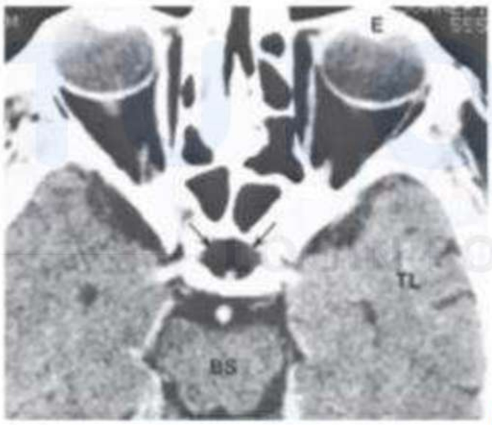


Fig: 1

## Pituitary adenoma 00:09:22

- Can lead to Hypo / Hyper Pituitary

## Classification of Pituitary Adenoma

| Micro Adenomas | Macro Adenomas |
|---|---|
| Size < 1cm | Size > 1cm |
| [Acidophilic / Basophilic] | Non Function Adenoma |

## Frequency of Adenomas of Anterior Pituitary

- Most common functional Adenomas of Posterior Pituitary – >26% of Functional Adenomas is Lactotrope
- Least common functional Adenoma – Thyrotrope
- Overall, most common Adenoma of pituitary is nonfunctional adenoma (27% of all types)

## Pituitary Adenoma

i. Microscopic View
  - Monomorphic Cells
  - Loss of reticulum Network

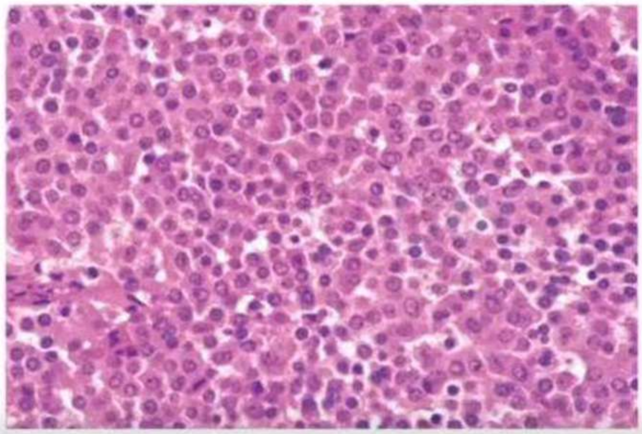
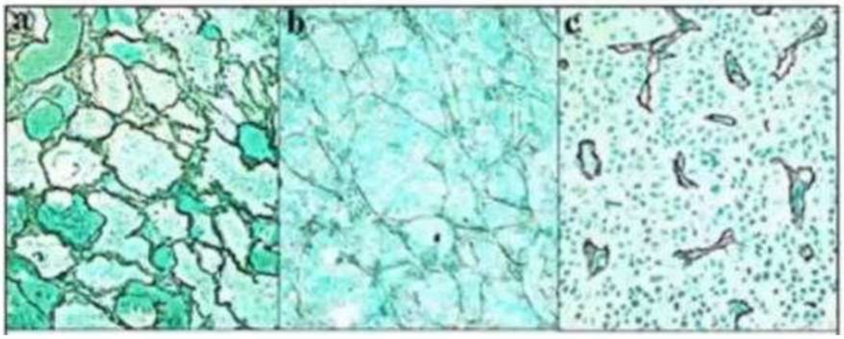


Fig: 2



Normal Hyperplasia Adenoma Fig: 3

## ACTH Adenoma

- Excess of ACTH and Cytokeratin which is a protein and appears Pink or H&E
- Crooke Hyaline change
- Can lead to Cushing's Disease

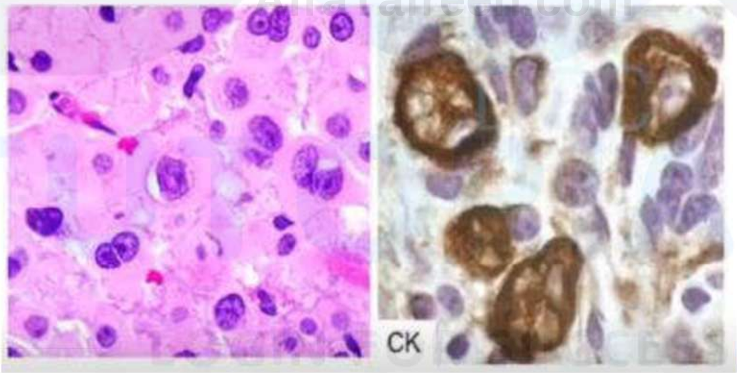


Fig: 4

## Prolactinoma

- Show Psammoma Bodies on microscopic view

## Molecular analysis 00:17:47

### Molecular Analysis of Adenoma

- Most common mutation – GNAS [codes for 2 chains of GTP]
- Other conditions where GNAS mutation occurs is Toxic Follicular Adenoma, Fibrous dysplasia of Bone
  - GNAS present on Chromosome 20q

i. Gain of Function Mutation

- GNAS – GH Adenomas
- PRKAR-1
  - a. Prolactinomas
  - b. GH Adenomas
- Cyclin O1 – Aggressive Adenomas
- HRAS – Pituitary Carcinomas

ii. Loss of Function Mutation

a. $MEN_1$

- Codes for Menin
- Prolactinoma
- GH Adenoma
- ACTH Adenoma

b. P27 [CDK $N_1B$] – ACTH Adenomas

c. AIP [Aryl Receptor Interacting Protein] – GH Adenomas [< 35 years]

d. RB gene – Aggressive Pituitary Adenomas

TUTORIALS LOGIN FOR SUCCESS

# BASICS OF SKIN

- **Pigmentary lesion**
  - Nevus
  - Melanoma
- **Inflammatory lesion**
  - Acute Inflammatory Dermatosis
    - i. Urticaria.
    - ii. Erythema Multiforma
  - Chronic inflammatory dermatosis
    - i. Psoriasis
    - ii. Lichen Planus
- **Bullous disorders**

**Tumor of skin**

- Benign
  - Epithelial
    - – Seborrheic keratosis
    - – Acanthosis Nigerians
    - – Appendageal
      - i. Cylindoma
      - ii.Trichilemmoma
      - iii. pilomatricoma
  - Dermal
    - Dermatofibroma (Benign)
    - Dermatofibrosarcoma protuberans. (Borderline to Malignant)
- Malignant SCC
  - BCC
  - Melanoma
- Cutaneous T cell lymphoma
  - Mycosis Fungicides / Sezary Syndrome

## Anatomy of skin. 00:07:32

### Layers of Epidermis

- Stratum Corneum- Most superficial Layer Fully keratinized
  - Anucleate dead cells layer
- Stratum Granulosum – Bluish Keratohyalin Granules
- Stratum Spinosum – Polygonal cells connected to each other by desmosomes seen as spines under ordinary microscope
  - Also called prickle cell layer
  - Dendritic cells present in stratum spinosum
- Stratum Basale – Basale cell layer -deepest layers of Epidermis
  - Single layer of columnar epithelial cells
  - Continuously Multiplying
  - Presence of Melanocytes
  - Attached to Basement membrane through Hemidesmosomes

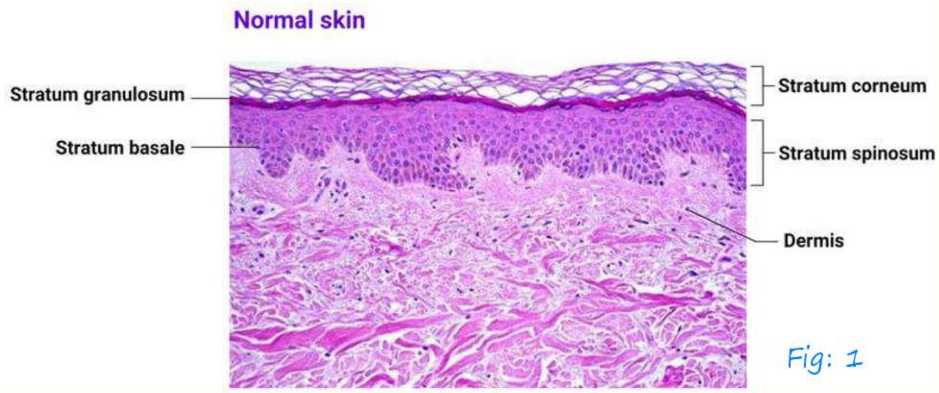

Normal skin
Stratum granulosum
Stratum basale
Stratum corneum
Stratum spinosum
Dermis

Fig: 1

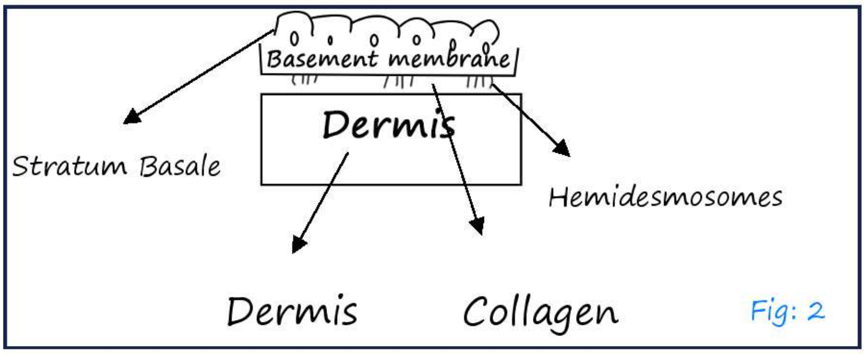

Basement membrane
Dermis
Stratum Basale
Hemidesmosomes
Dermis
Collagen

Fig: 2

- **Note**: In Hands & Feet additional layer called stratum lucidum is present between Stratum Granuloma and carenum

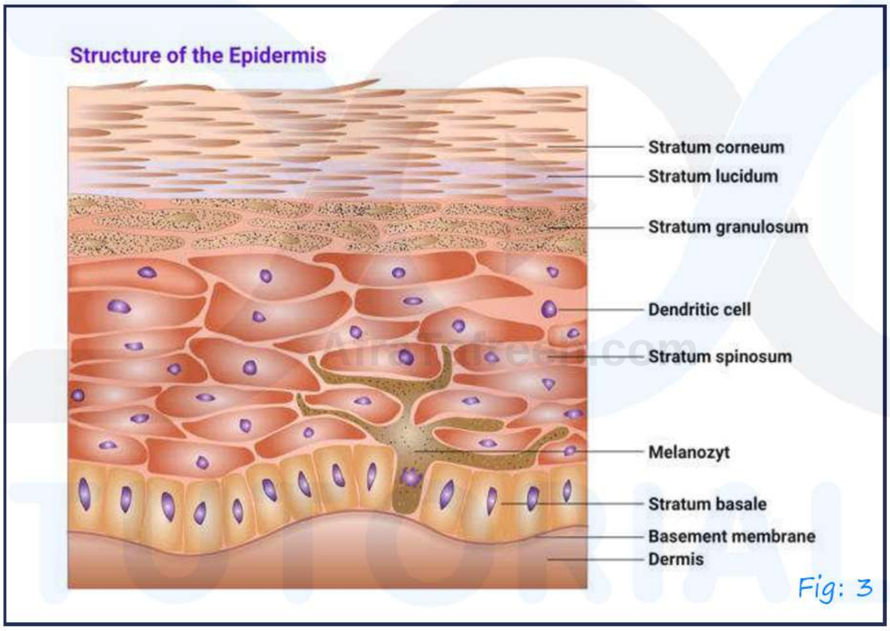

Structure of the Epidermis
Stratum corneum
Stratum lucidum
Stratum granulosum
Dendritic cell
Stratum spinosum
Melanozyt
Stratum basale
Basement membrane
Dermis

Fig: 3

TUTORIALS LOGIN FOR SUCCESS

## Dermis

- Dermis is divided into two layers
- Papillary Dermis: Superficial layer which contains loose Areolar tissue, superficial capillaries &Nerve endings
- Reticular Dermis: Deep layer containing collagen Elastic fiber appendages
- Dermis is attached to basement membrane by collagen 7 (non fibrillar collagen)

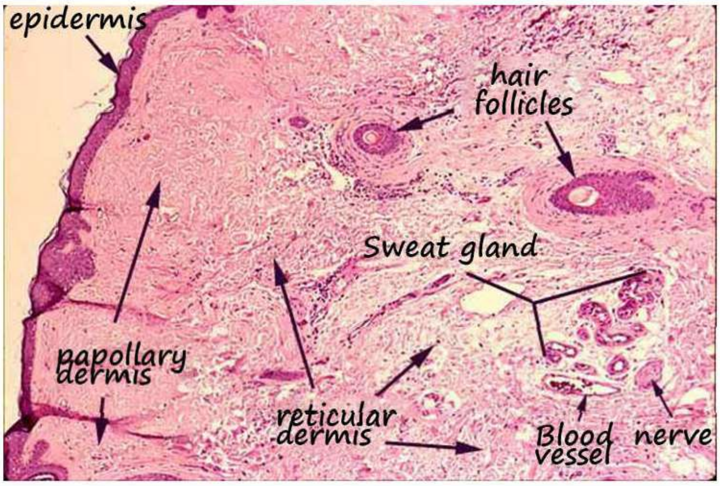

epidermis
hair follicles
Sweat gland
papollary dermis
reticular dermis
Blood vessel
nerve

Fig: 4

- Epidermis folds into dermis in the form of down growths called rete ridges
- Dermal papillae projects as finger like processes into the epidermis

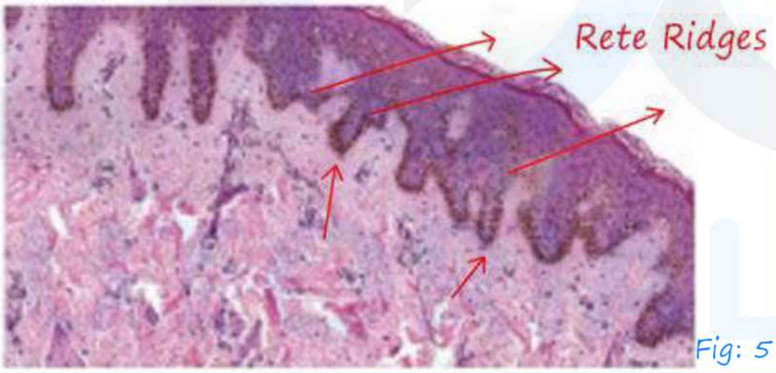

Rete Ridges

Fig: 5

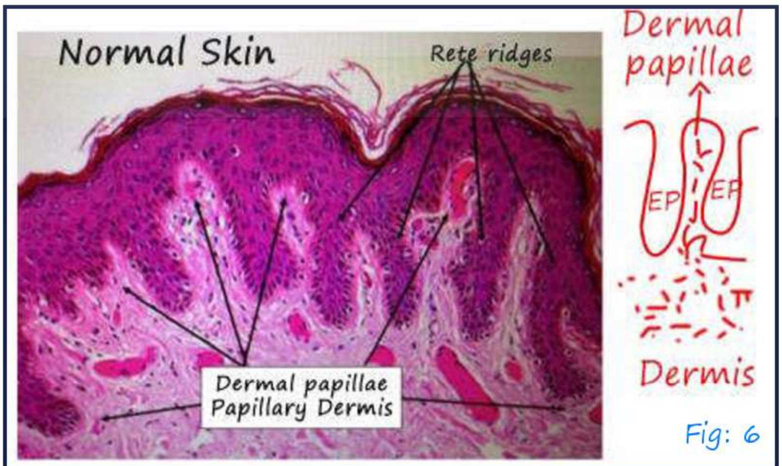

Normal Skin
Rete ridges
Dermal papillae
Papillary Dermis
Dermal papillae
EP
EP
Dermis

Fig: 6

## Appendages

- Hair
- Nails
- Glands
  - Sweat
    - Eccrine
      - Involved in temperature i.e., sweat
    - Apocrine
      - Specialized sweat Glands
      - Secretions is odoriferous With a secondary sexual Significance (pheromone)
      - Abundant Pink Cytoplasm with apical anouting
  - Sebaceous

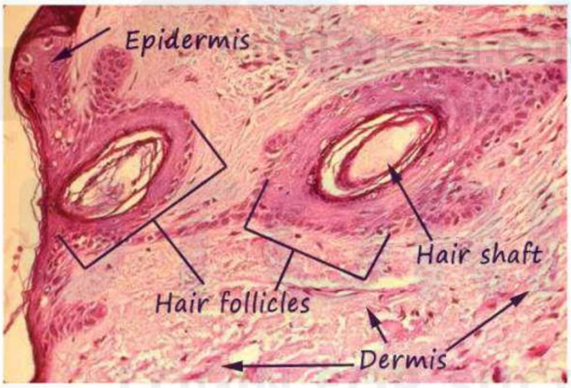

Epidermis
Hair shaft
Hair follicles
Dermis

Fig: 7

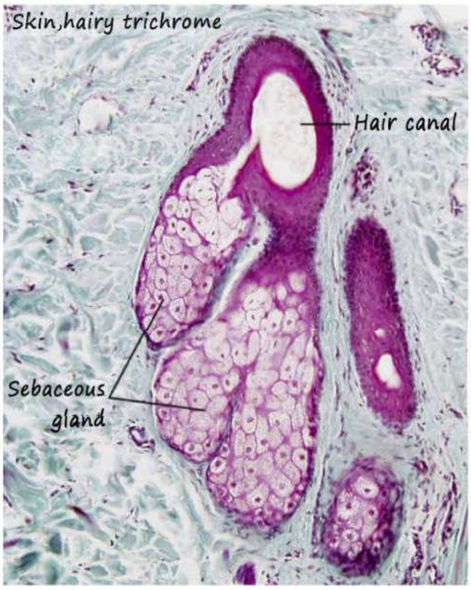

Skin,hairy trichrome
Hair canal
Sebaceous gland

Fig: 8

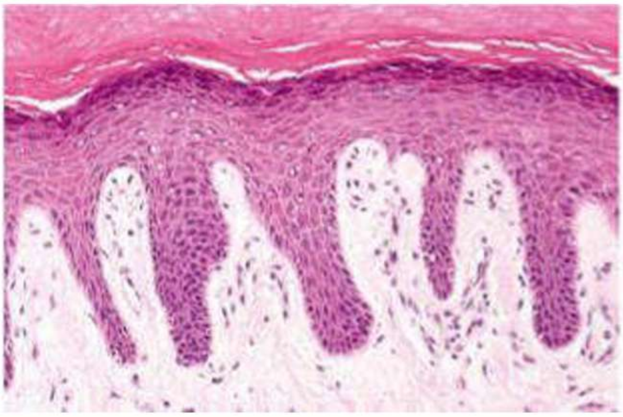


Fig: 9

- Pilosebaceous Glands
- Sebaceous Glands opening into Hair follicles

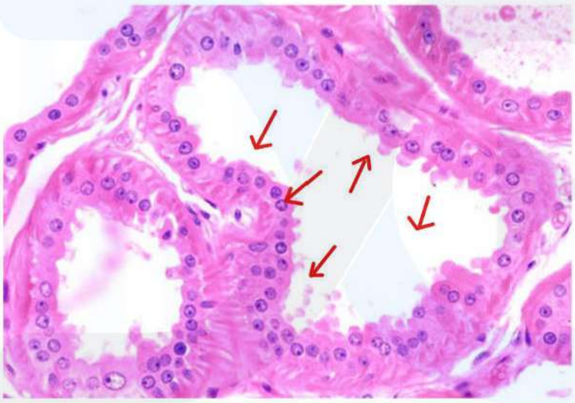
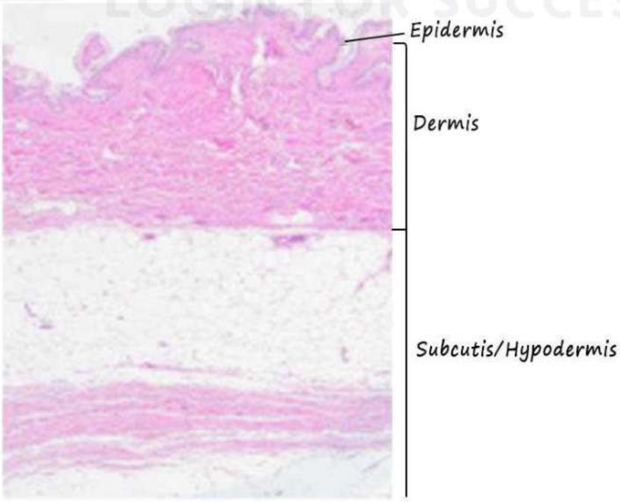


Fig: 10

## Subcutis or Hypodermis


Epidermis
Dermis
Subcutis/Hypodermis

**Consists of Fat (Adipose) tissue** Fig: 11

## Terminologies

- Petechial – 1-2 mm
- Purpura – 3-10 mm
- Ecchymosis - >1 cm

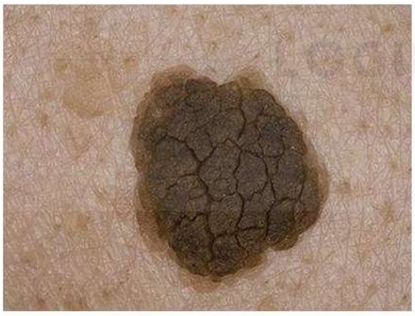
No Balancing

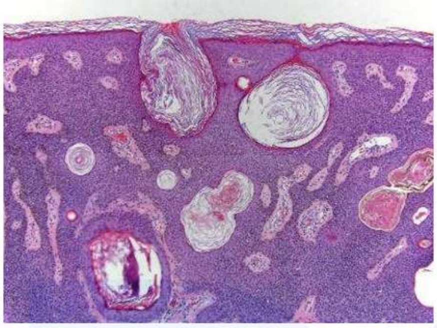
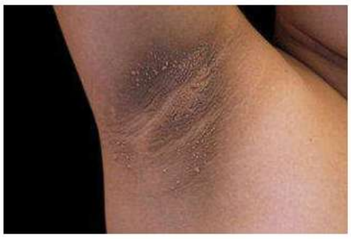
| Flat lesion | | Elevated lesion | | Fluid filled | |
|---|---|---|---|---|---|
| < 5 mm | > 5 mm | <5mm | >5mm | <5mm | >5mm |
| Macule | Patch | Papule | Nodule | Vesicle | Bulla |

- Acanthosis → Thickening of Epidermis
- Hyperkeratosis → Thickening of Stratum cornuem
- Hypergranulosis → Thickening of Granular layer
- Para keratosis Retention of Nuclei in cells of Stratum corneum
- Thinning of Supra papillary dermis → Predisposes to recurrent Capillary Hemorrhages in the form of Petechial purpura
- Elongation of rate Ridges – Seen in Psoriasis
- Flattening of Rate Ridges – seen in systemic Sclerosis

DOC TUTORIALS LOGIN FOR SUCCESS

# TUMORS OF SKIN

<table>
<tr><th>Benign</th><th>Appendigeal</th></tr>
<tr><td>i. Seborrheic Keratosis<br>ii. Acanthosis Nigricans</td><td>i. Cylindroma<br>ii. Trichillemmoma seen in cowden syndrome (PTEN mutation)<br>iii. Pilomatricoma</td></tr>
<tr><td>Sebarrhic keratosis</td><td>Acanthosis Nigricans</td></tr>
<tr><td colspan="2">← i. Mutation of FGFR3 →<br>← ii. Lesser tresat sign →</td></tr>
<tr><td colspan="2">Omnious sign internal Malignancy<br>Development of new lesions preexisting ones<br>Increase in size & become symptomatic</td></tr>
<tr><td>Gross→stuck appearance seborrheic keratosis<br><br>Histology<br>i. Horn cysts- communicating With Epidermis</td><td>Acantosis Nigricans is a paraneoplastic Manifestation of Gastric cancer also seen in Diabetes due to Increase IGF secretion<br>Gross: velvety Appearance seen at flexural surfaces Back of Neck, Axilla, Groin</td></tr>
</table>

| | |
|---|---|
| ii. Pseudo-Horn cyst or<br>- Invagination cyst→Do not communicate with Epidermis<br> | <br>**Histology**<br>i. Increased melanin Pigmentation of Basal cells<br>ii. Papillomatosis of Epithelial cells |

## Appendegial Tumors 00:07:53

**I. Cylindroma -**

i. occurs in scalp also called Turban tumor

ii. Mutation of CYCLD gene (tumor suppenos gene)
Deletion of CYLD causes over activation of NFKB
Which causes proliferation of Basal Cells

iii. Can show Eccrine or Apocrine differentiation.

**Microscopy -**

i. Proliferation of Basaloid cells fitting in a Jigsaw puzzle manner.

ii. Separated by a Basement membrane like material

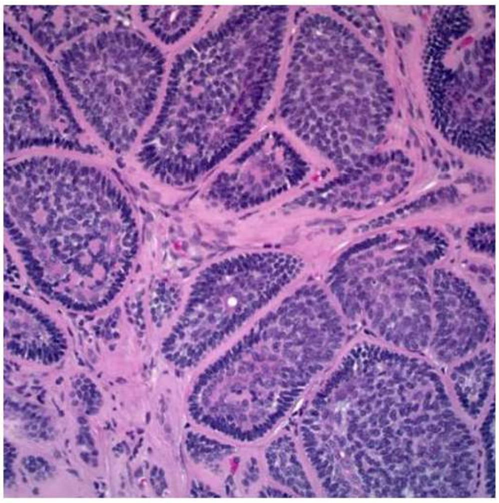
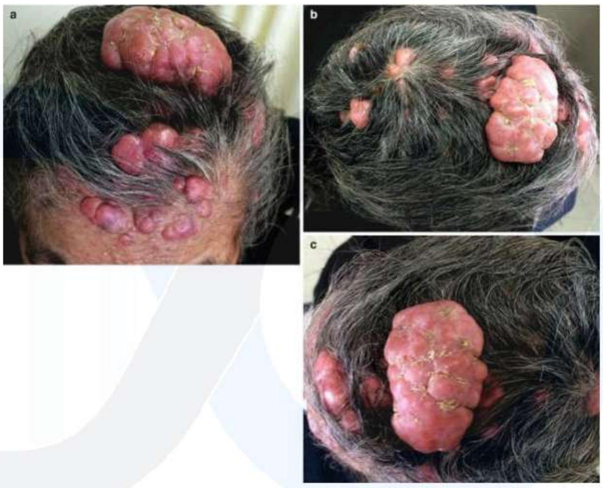


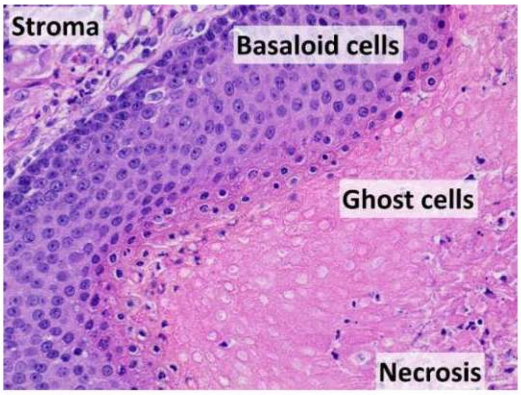
Fig: 1



Cylindroma turban tumor Fig: 2

## Pliomatricoma

- Show hair follicle differentiation
- Mutation of β-catenin
- On Histology –proliferation of Basal cells & Ghost cells (squamous cells without nuclei)



Stroma
Basaloid cells
Ghost cells
Necrosis

Fig: 3

## Malignant Tumors. 00:11:17

### Basal cell carcinoma (BCC)

- Commonest malignant tumor of skin
- Arises from Basal cell layer of Epidermis
- Locally aggressive, but metastascs does not occur.
- Hence called Rodent ulcer.

### GORLIN syndrome

i. Mutation BCC syndrome

ii. Mutation of PATCHED gene

iii. Associated with over activation of sonic Hedge Hog (SHH) pathway

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LOGIC FOR SUCCESS

### Histology :

i. Peripheral Palisading of tumor cells

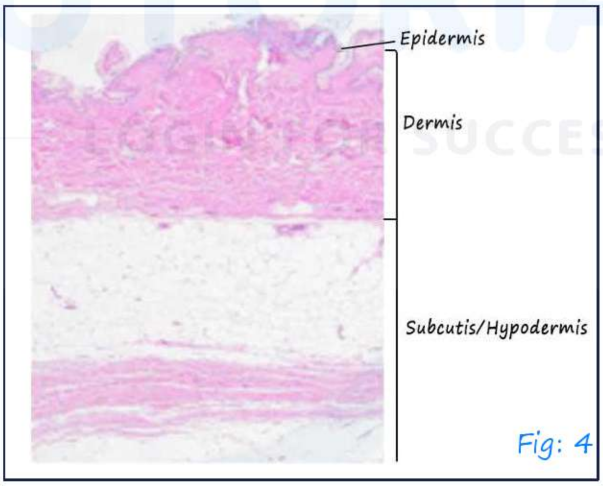


Fig: 4

ii. when tumors cells infiltrate into dermis, the stroma around them separates forming Retraction artifact due to mutation in SHH pathway

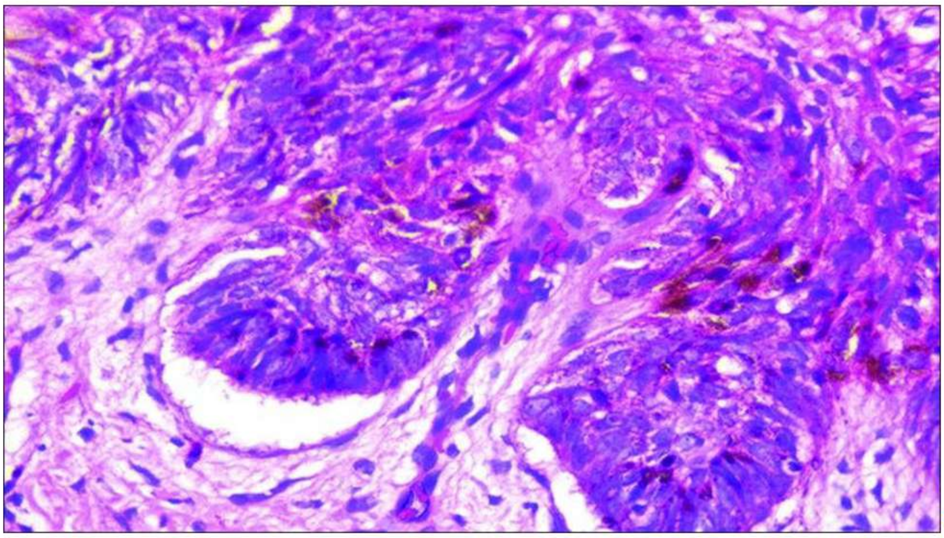


Fig: 5

## Squamous cell carcinoma scc

- Arises from Squamous cells (keratinocytes)
- Spreads locally & also metastasizes to regional lymph nodes

## Predisposing factors

i. Exposure to sun (U-V Rays)

ii. Ingestion of arsenicals

iii. Chronic Ulcer

iv. HPV 5,8 strong association

[HPV also causes Epidermodysplasia verruciformis]

## Precusior lesions of scc

i. Xeroderma pigmentosa

ii. Bowen's Disease

iii. Actinic Keratosis: Cause-sun exposure, Arsenic Exposure

TUTORIALS LOGIN FOR SUCCESS

## On Histology shows

i. Hyperperatosis

ii. Dysplasia

iii. Elastosis (increases Elastic fibres) in upper dermis

Gross: sand paper like appearance of skin

## Microscopy of scc

- Well differentiated scc shows keratin pearls

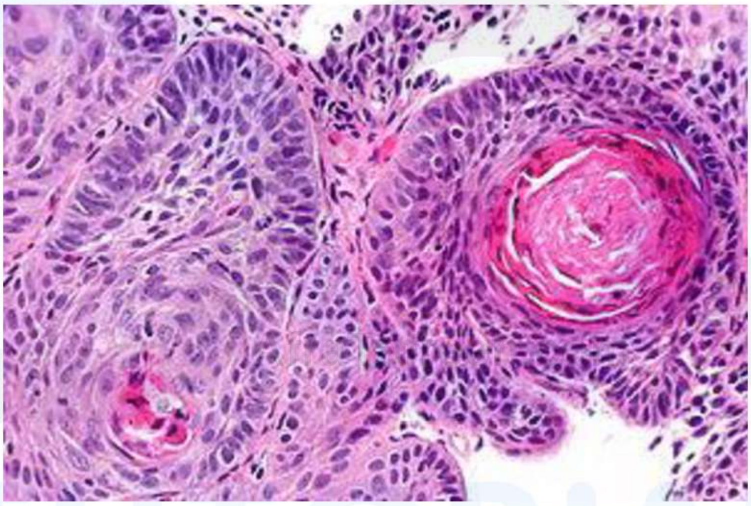


Fig: 6

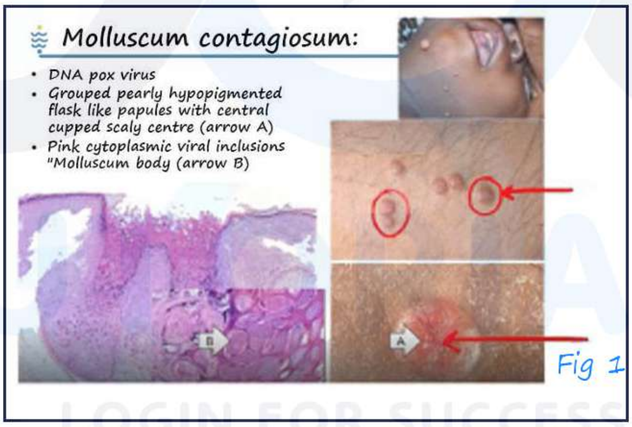
# INFECTIONS OF SKIN

Infection of skin

- Molluscum contagiosum
- Verruca
  - Verruca plana
  - Verruca Vulgaris

## Molluscum Contagiosum 00:00:57

- Caused by Pox Virus
- Multiple pearly white, dome-shaped papules, umbilicated centrally



**Molluscum contagiosum:**

- DNA pox virus
- Grouped pearly hypopigmented flask like papules with central cupped scaly centre (arrow A)
- Pink cytoplasmic viral inclusions "Molluscum body (arrow B)

Fig 1

- In children, Face is most commonly involved

### Biopsy Findings

i. Crater like lesion

ii. Cells containing eosinophilic intra cytoplasmic inclusion bodies called molluscum Henderson Peterson Bodies containing Viral Particles

- These inclusions Displace Nuclei to the periphery

Molluscum bodies are present (large cells with cytoplasmic, faintly granular eosinophilic inclusions that displace nuclei and contain viral particles) marked with arrow.

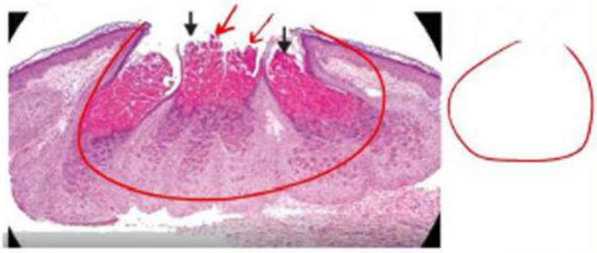


Fig 2

## Verruca 00:02:20

- Caused by Human papilloma virus infection'
- Commonly in children & young adults
- Verruca Vulgaris -> M/C Type
- Verruca plana -Flat wart
- Verruca plantar is Palmoplantar Verruca also called Myrmecia

AfraTafreen.com
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LOGIN FOR SUCCESS

### Histopathology

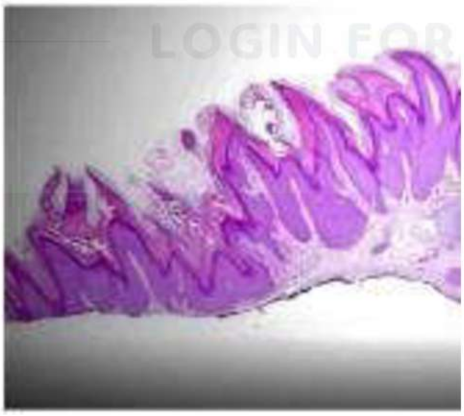
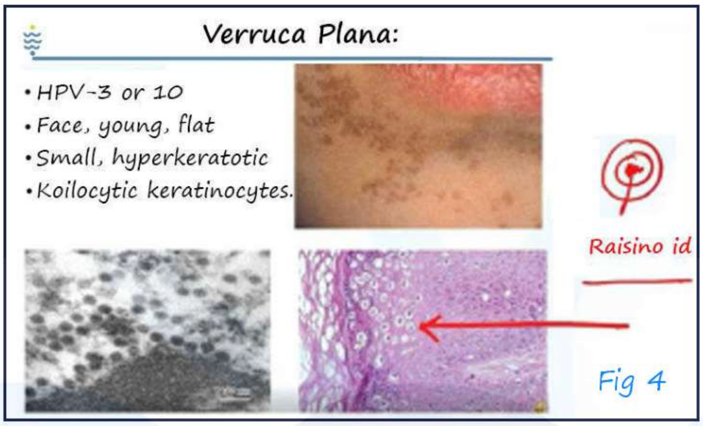


Fig 3

- Hyperkeratotic Epidermis with Hill shaped papillomatosis seen in Verruca Vulgaris & Palmoplantar Verruca (Absent in Verruca plana)

- Koilocytosis
  i. Large Squamous cells with Perinuclear Halo and Rainsinoid nucleus Characteristic of HPV infection



Verruca Plana:

- HPV-3 or 10
- Face, young, flat
- Small, hyperkeratotic
- Koilocytic keratinocytes.

Raisino id

Fig 4

# SALIVARY GLAND BASICS

## Main function: Production of saliva 00:00:05

Major Glands (90% saliva)

- Parotid
- Submandibular
- Subligual

Minor Salivary Glands (10% saliva)

↓

600-1000 present throughout oral cavity

- Just made up of acini
- Anti-hard palate givgiver near alveolar ridges → no minor glands present

DX TUTORIALS
LOGIN FOR SUCCESS

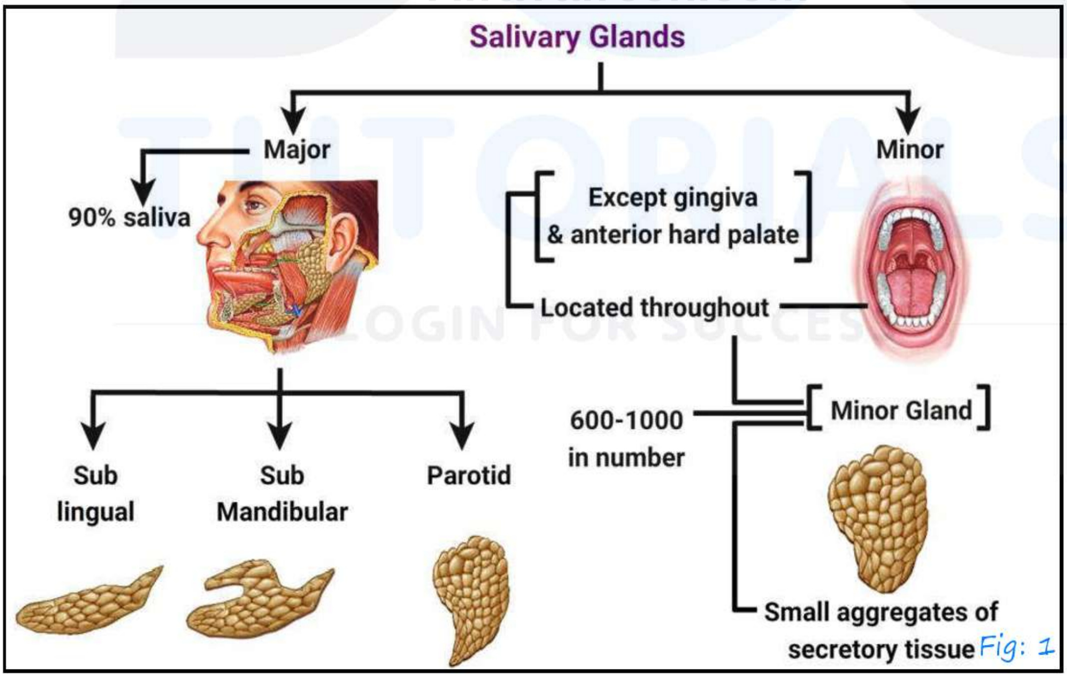

Salivary Glands
Major
Minor
90% saliva
Except gingiva & anterior hard palate
Located throughout
600-1000 in number
Minor Gland
Sub lingual
Sub Mandibular
Parotid
Small aggregates of secretory tissue

Fig: 1

## Secretory cells → cluster together to forms acinus

Serous
parotid
Submandibular
bublingual

Mucinous
Minor salivary glands
Reception: von elner glands (serous)

- Submandibular: mixed but mostly serous
- Sublingual: Mixed but mostly mucinous

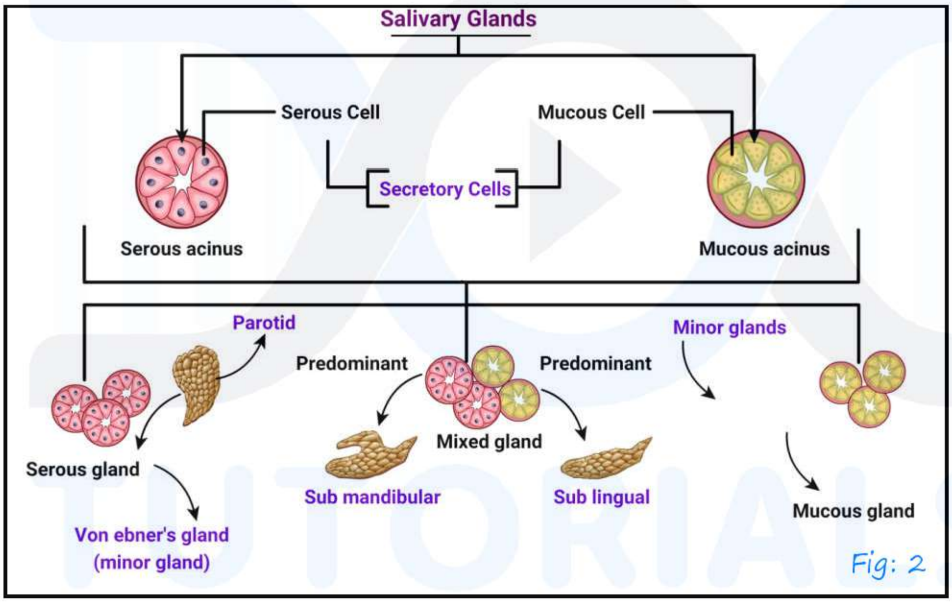

Salivary Glands
Serous Cell
Mucous Cell
Secretory Cells
Serous acinus
Mucous acinus
Parotid
Minor glands
Predominant
Predominant
Serous gland
Mixed gland
Sub mandibular
Sub lingual
Mucous gland
Von ebner's gland
(minor gland)

Fig: 2

## Secretion outflow pathway: DUCT

- Acini (Forms secretion) → intercalated ducts

↓

Striated ducts (Epithelium is throcum into folds with abundant mitochondria)

↓

Secretory ducts → out

(Inter lobular)

And

(Inter lobar)

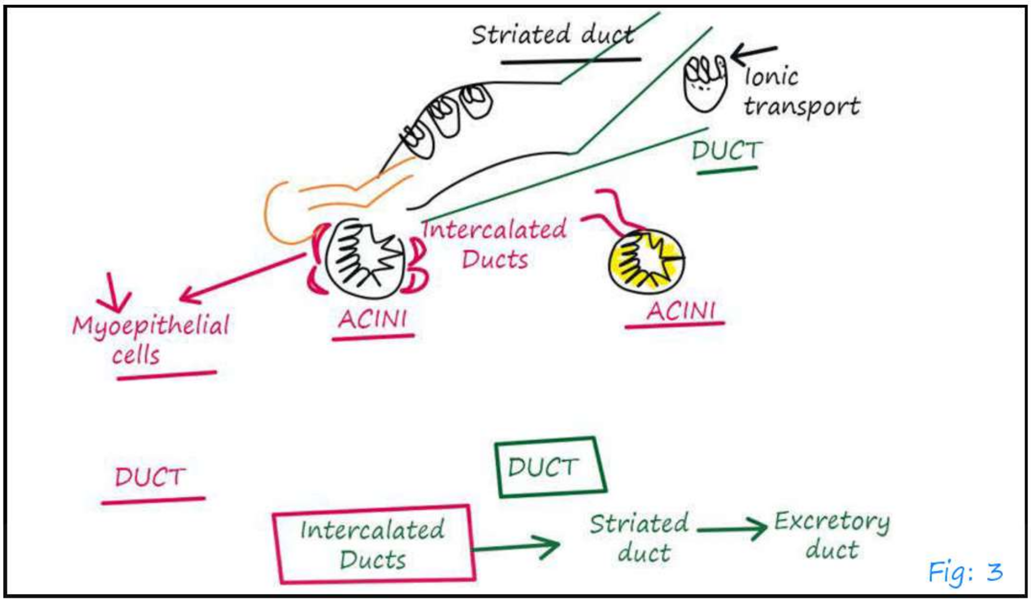

Striated duct
Ionic transport
DUCT
Intercalated Ducts
Myoepithelial cells
ACINI
ACINI
DUCT
DUCT
Intercalated Ducts
Striated duct
Excretory duct

Fig: 3

**Secretory**

- Berous
- mucinous

- Myoepithelial cells contract to push secretion out.

TUTORIALS
LOOK FOR SUCCESS

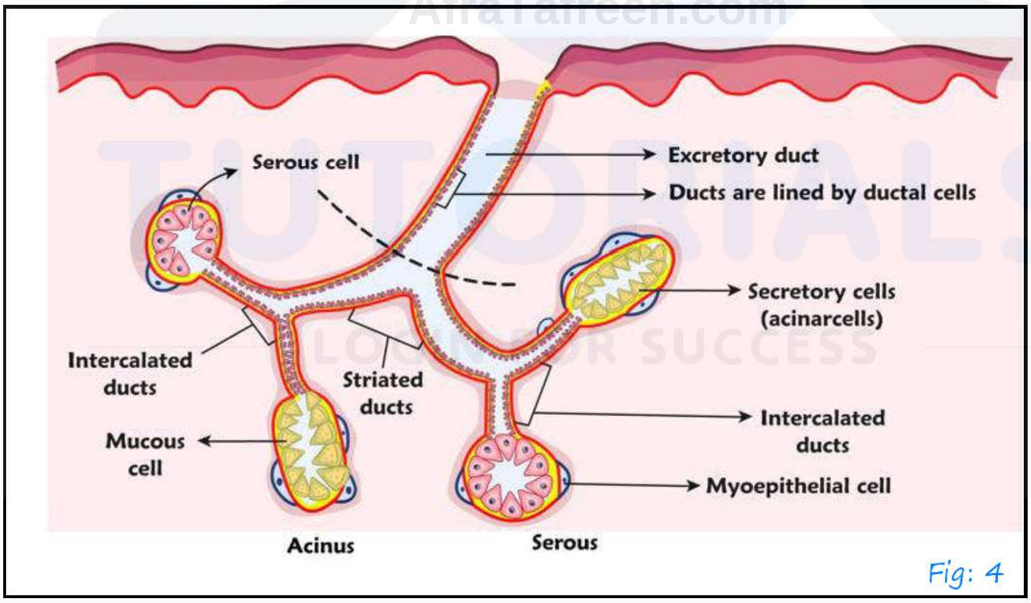

Serous cell
Excretory duct
Ducts are lined by ductal cells
Secretory cells (acinarcells)
Intercalated ducts
Striated ducts
Mucous cell
Intercalated ducts
Myoepithelial cell
Acinus
Serous

Fig: 4

## Structure of salivary glands 00:14:55

- Every salivary gland has lobe
- Lobe is divided into lobules

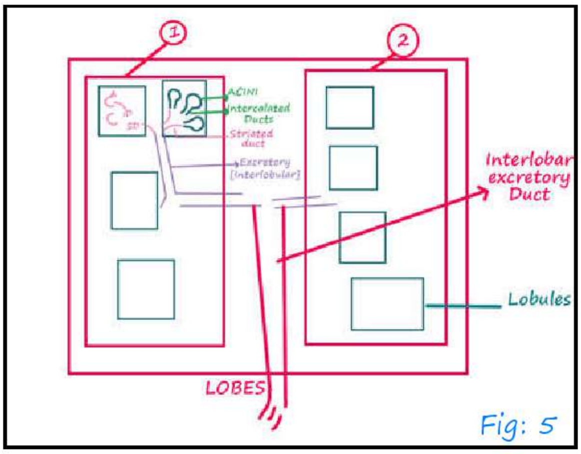

①
②
ACINI
Intercalated Ducts
Striated duct
Excretory [interlobular]
Interlobar excretory Duct
Lobules
LOBES

Fig: 5

- Every lobule has a lat of acini

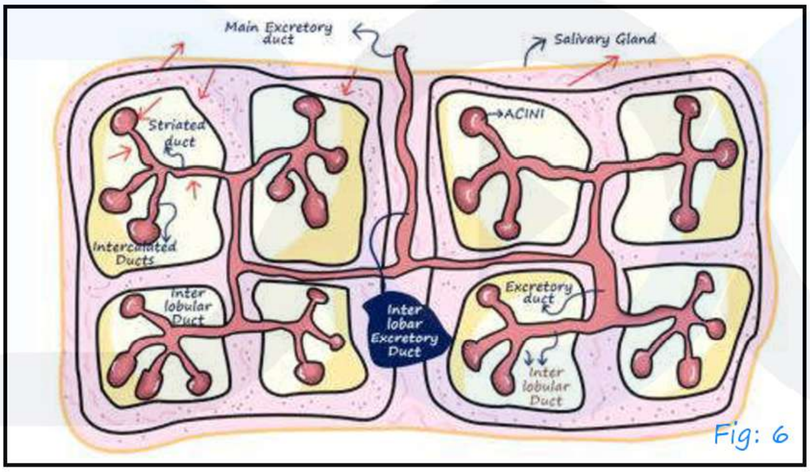

Main Excretory duct
Salivary Gland
Striated duct
ACINI
Intercalated Ducts
Inter lobular Duct
Inter lobar Excretory Duct
Excretory duct
Inter lobular Duct

Fig: 6

- Biopsy is usually taken from a lobule

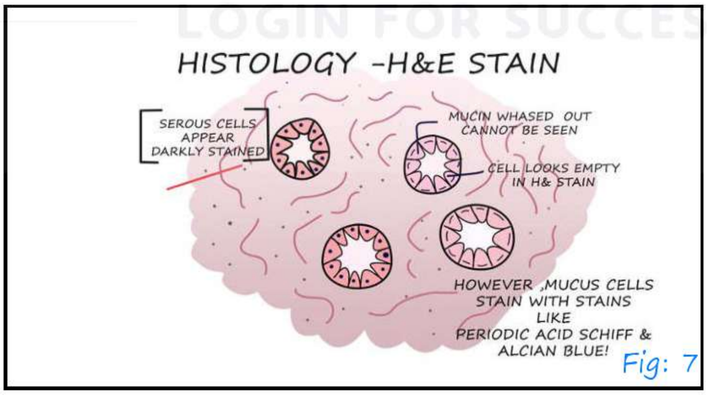

HISTOLOGY -H&E STAIN
SEROUS CELLS APPEAR DARKLY STAINED
MUCIN WHASED OUT CANNOT BE SEEN
CELL LOOKS EMPTY IN H& STAIN
HOWEVER ,MUCUS CELLS STAIN WITH STAINS LIKE PERIODIC ACID SCHIFF & ALCIAN BLUE!

Fig: 7

- Mucinous cells – seen on PAS stain clearly
- Striated ducts are lined by columnar epithelium
- ICDs are lined by cuboidal epithelium.

# SALIVARY GLAND TUMORS

## Salivary gland tumors 00:00:30

- Histological classification of common benign and malignant salivary gland tumors

| Benign Tumors | Malignant Tumors |
|---|---|
| Pleomorphic adenoma (m.c) | Mucoepidermoid carcinoma |
| Warthin tumor's | Adenocarcinoma NOS |
| Oncocytoma | Acinic cell carcinoma |
| Other adenoma (Basal cell adenoma) | Adenoid cystic carcinoma |

**Benign Neoplasms**

## Pleomorphic Adenoma 00:03:10

- Commonest neoplasm of salivary gland
- In females,40-60 years
- Most common salivary gland involved: Parotid > Submandibular > Minor salivary gland.
- Shows both epithelial (ductal cells and myoepithelial cells) and mesenchymal differentiation. Thus, knows as mixed tumor
- Carcinoma arising in pleomorphic adenoma is called carcinoma, example pleomorphic adenoma.

- Proliferation of epithelial cells is due to mutation of epithelial cells is t(8,12) PLAG-1 fuses with HMGA
- The malignant component of Ca ex pleomorphic adenoma is most often adenocarcinoma not otherwise specified

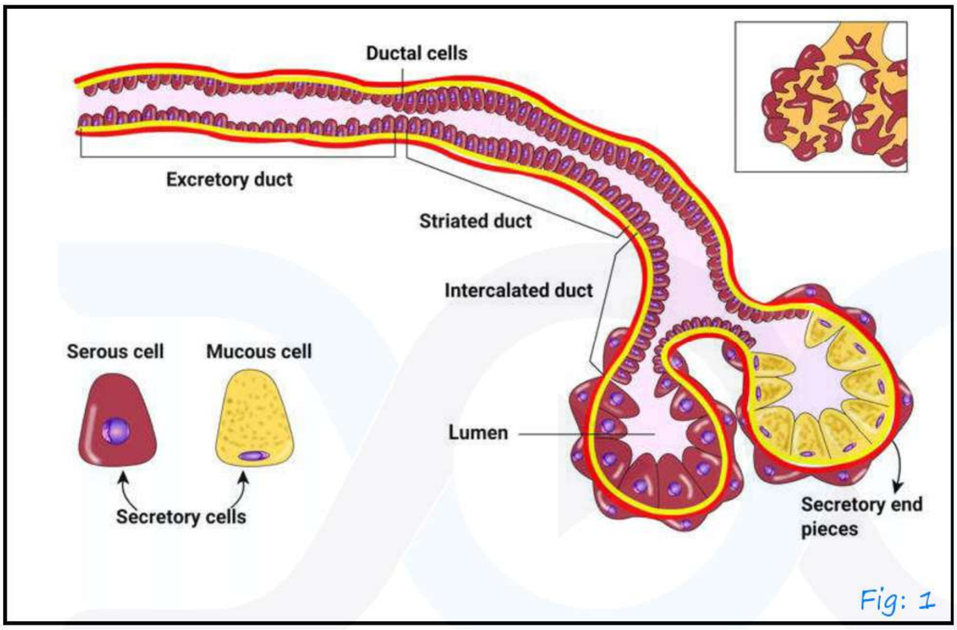

Ductal cells
Excretory duct
Striated duct
Intercalated duct
Serous cell
Mucous cell
Secretory cells
Lumen
Secretory end pieces

Fig: 1

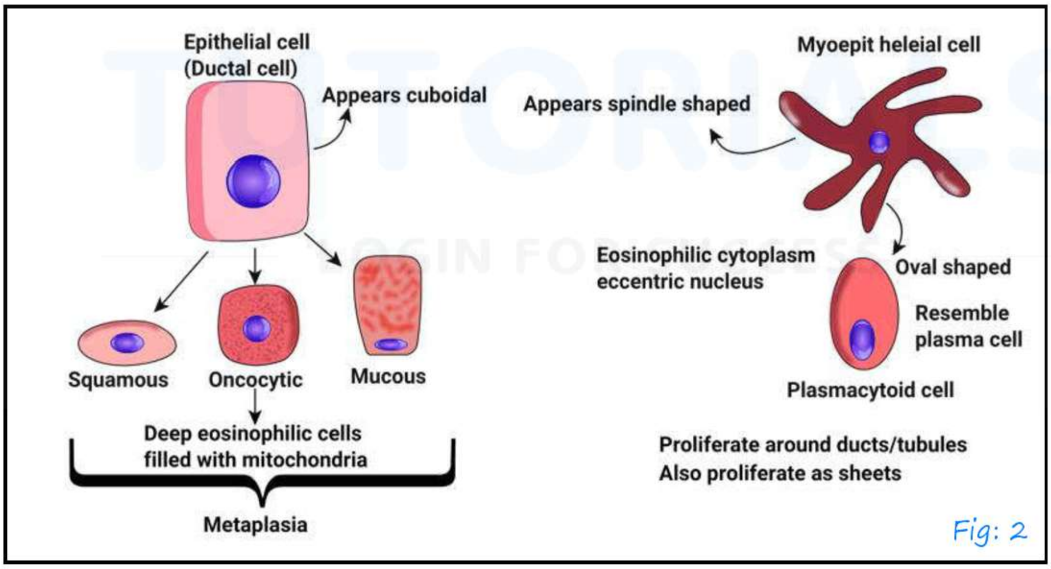

Epithelial cell (Ductal cell)
Appears cuboidal
Myoepit heleial cell
Appears spindle shaped
Squamous
Oncocytic
Mucous
Deep eosinophilic cells filled with mitochondria
Metaplasia
Eosinophilic cytoplasm eccentric nucleus
Oval shaped
Resemble plasma cell
Plasmacytoid cell
Proliferate around ducts/tubules
Also proliferate as sheets

Fig: 2

- **Chondromyxoid stroma**
- **Complete excision is mandatory.**

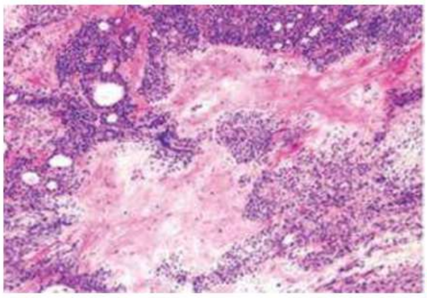
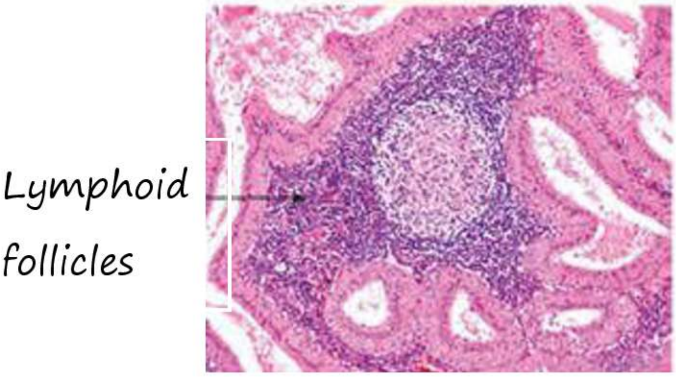


Fig: 3

## Warthin's Tumor 00:21:05

- Also known as papillary cystadenoma lymphomatosum
- Second most common benign salivary gland tumor (after pleomorphic adenoma)
- More common in males ,smoking
- Common tumor of parotid gland with double layer of epithelial cells resting on dense lymphoid stroma. Papillae formation.
- Metaplasia of tissue.
- Ducts become cystically dilated showing oncocytic metaplasia
- Surface palisading of oncolytic columnar cells are seen
- FNAC – murky fluid



Warthin's tumor

Fig: 4

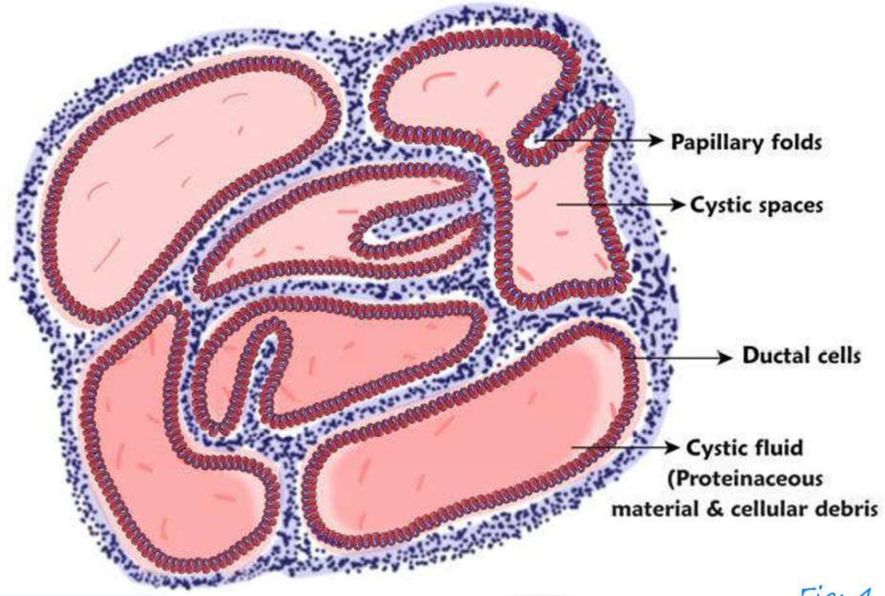

Papillary folds
Cystic spaces
Ductal cells
Cystic fluid
(Proteinaceous
material & cellular debris

Fig: 4

# MALIGNANT TUMORS

## Muco-epidermoid carcinoma 00:00:33

↓ ↓

Mucus Squamoid

- Arises from reserve cells (Pluripotent cells) in excretory duct
- Mutation in reserve cells activates → NOTCH Pathway (MECT – MAML$_2$)
- Cells present together in muco epidermoid:

  1.Mucus cells → Mucicarmine stain positive

  2.Intermediate cells

  3.Squamous cells: Higher the use of squamous cells higher the grade of tumor

- Keratinization is usually not a feature
- Can occur in any age group
- No sex predilection
- t (11:19) – MECT 1 – MAML 2 fusion
- Most common malignant salivary gland tumor
- Most common site – parotid
- Most common tumor of minor salivary gland
- Most common oral – children

## Adenoid cystic carcinoma 00:08:43

- Second most common malignant tumors of salivary gland
- Mostly in minor salivary glands especially submandibular
- Can occur in palate, breast, larynx, prostate

**Perineural invasion → Pain (low grade and dull)**

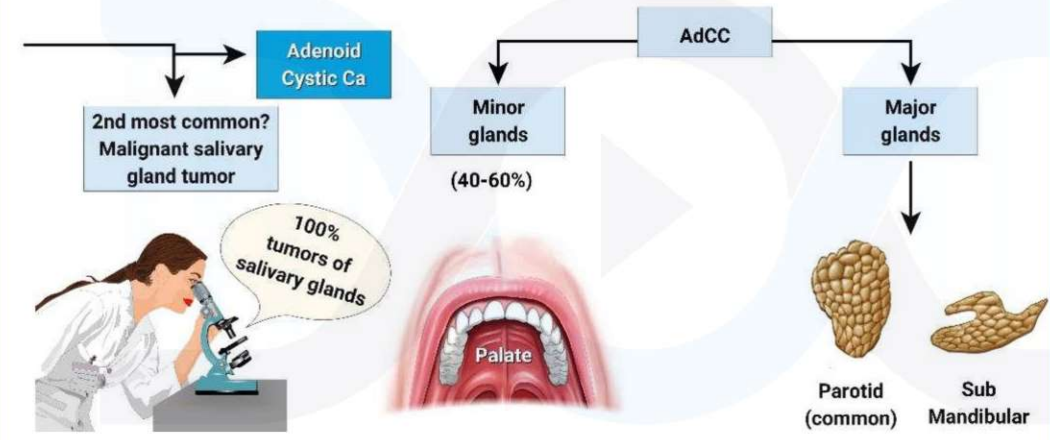

Adenoid Cystic Ca
2nd most common? Malignant salivary gland tumor
100% tumors of salivary glands
AdCC
Minor glands
(40-60%)
Palate
Major glands
Parotid (common)
Sub Mandibular

Fig: 1

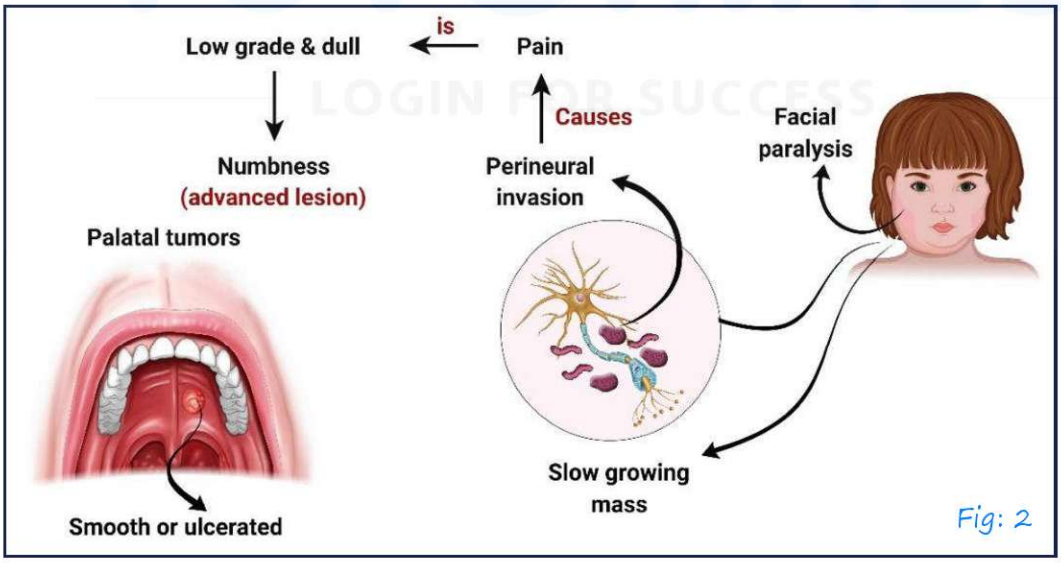

Low grade & dull
is
Pain
Causes
Numbness (advanced lesion)
Perineural invasion
Facial paralysis
Palatal tumors
Slow growing mass
Smooth or ulcerated

Fig: 2

- Arises from ductal or myoepithelial cells
- Ulcerated mass of palate → common presentation

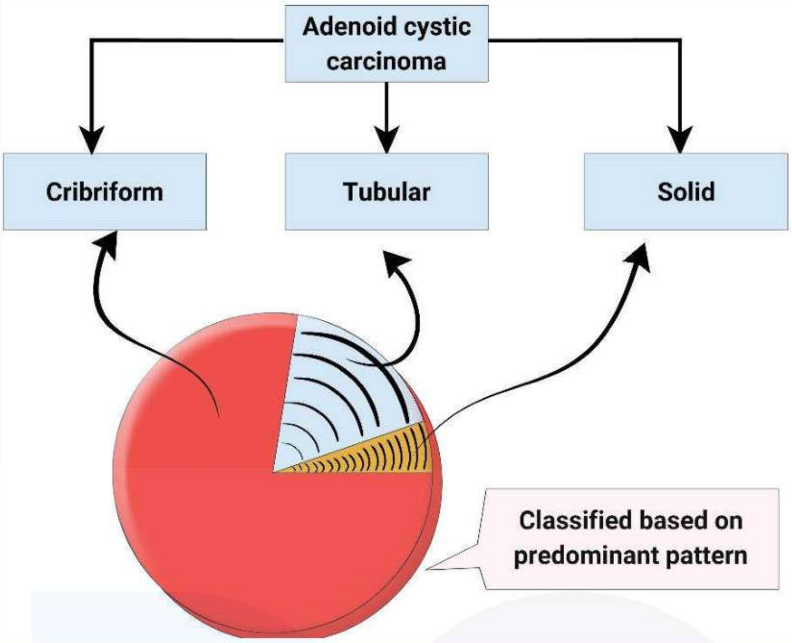
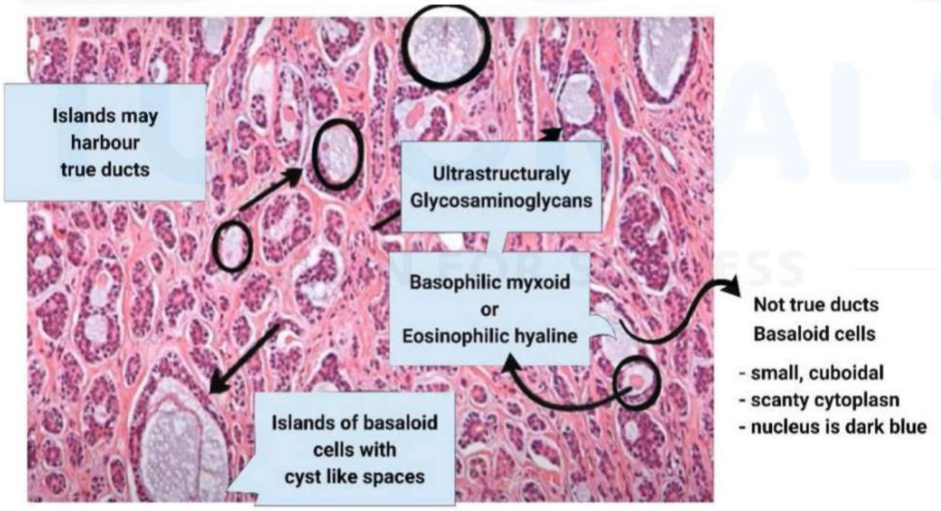

Adenoid cystic carcinoma
Cribriform
Tubular
Solid
Classified based on predominant pattern

Fig: 3

3 patterns

- Cribriform
- Tubular
- solid


Islands may harbour true ducts
Ultrastructuraly Glycosaminoglycans
Basophilic myxoid or Eosinophilic hyaline
Not true ducts Basaloid cells
- small, cuboidal
- scanty cytoplasn
- nucleus is dark blue
Islands of basaloid cells with cyst like spaces

Classified based on predominant pattern Fig: 4

## Cribriform pattern:

- Malignant hyperchromatic arranged around cystic spaces

↓

Swiss cheese / cookie cutter appearance

- Cysts are not true ducts: glycosaminoglycans
  - Tubular pattern

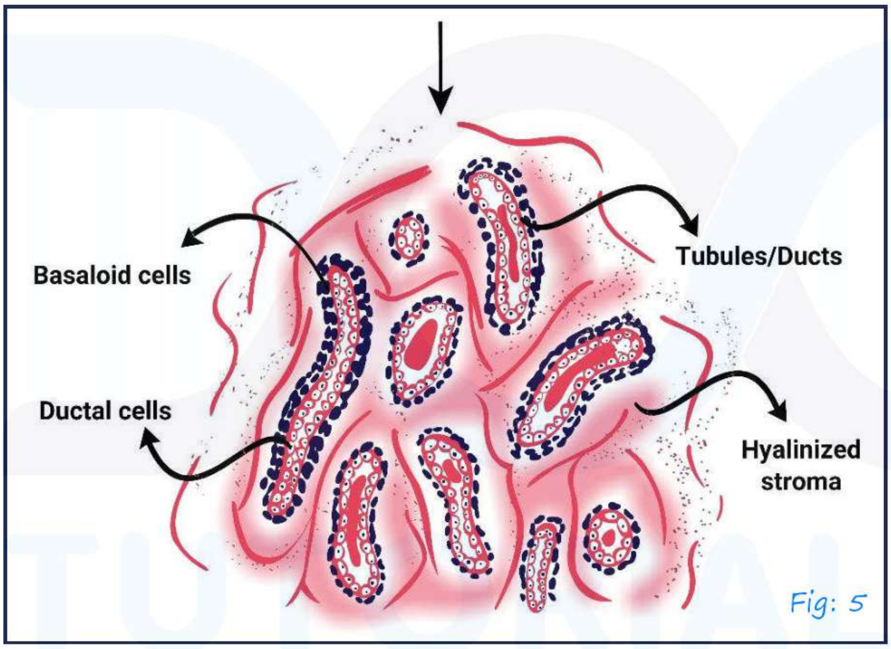

Basaloid cells
Tubules/Ducts
Ductal cells
Hyalinized stroma

Fig: 5

- Ducts lined by flattered cells surrounded by basaloid cells
  - Solid pattern

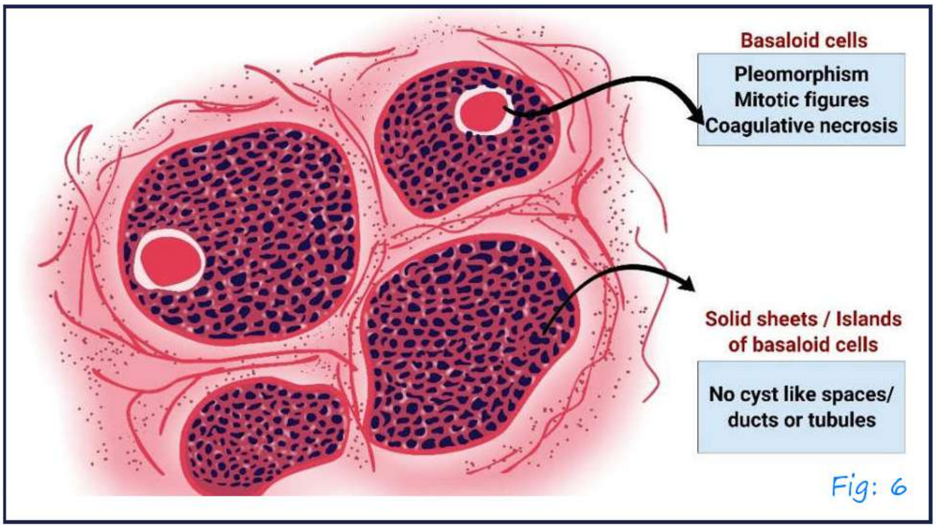

Basaloid cells
Pleomorphism
Mitotic figures
Coagulative necrosis
Solid sheets / Islands of basaloid cells
No cyst like spaces/ ducts or tubules

Fig: 6

- Small and hyperchromatic nuclei
- No cyst like spaces / ducts or tubules

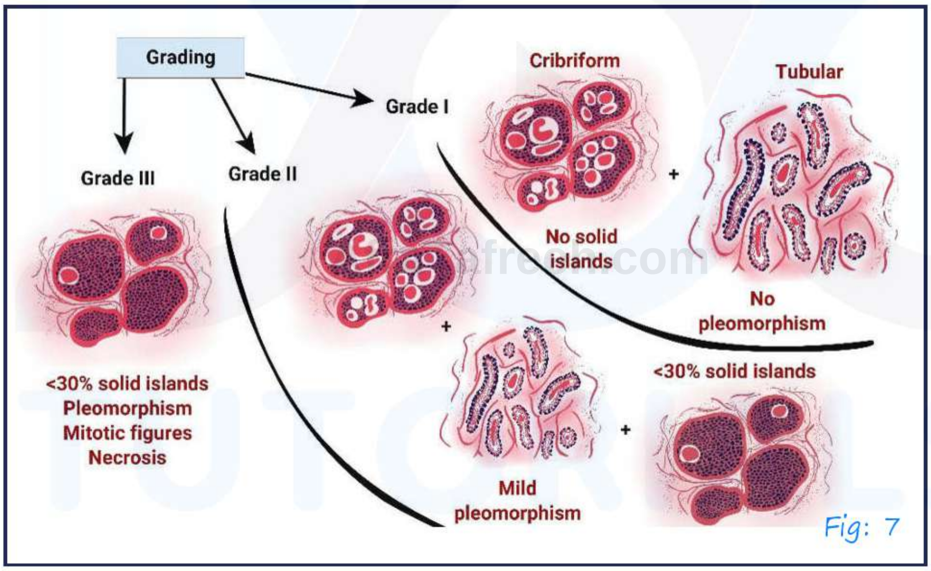

Grading
Grade I
Grade II
Grade III
Cribriform
Tubular
No solid islands
No pleomorphism
<30% solid islands
Mild pleomorphism
<30% solid islands
Pleomorphism
Mitotic figures
Necrosis

Fig: 7

## Grading:

- Grade I – No solid pattern islands
  No pleomorphism
- Grade II – < 30% solid islands
  Mild pleomorphism
- Grade III → 30% solid islands
  Pleomorphism, mitotic figures

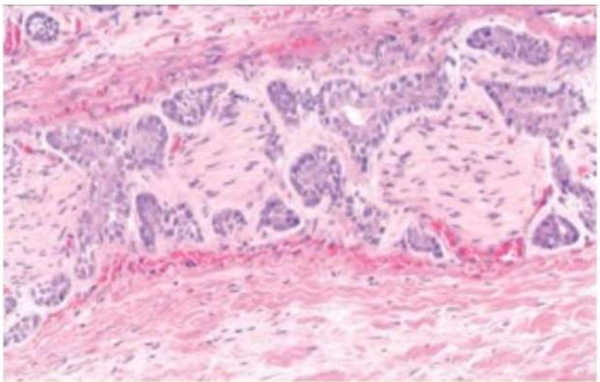


Fig: 8

**Mutations in ACC:**

t (6;9) translocations and chromosome 6 deletions→ Myb – NFIB fusion

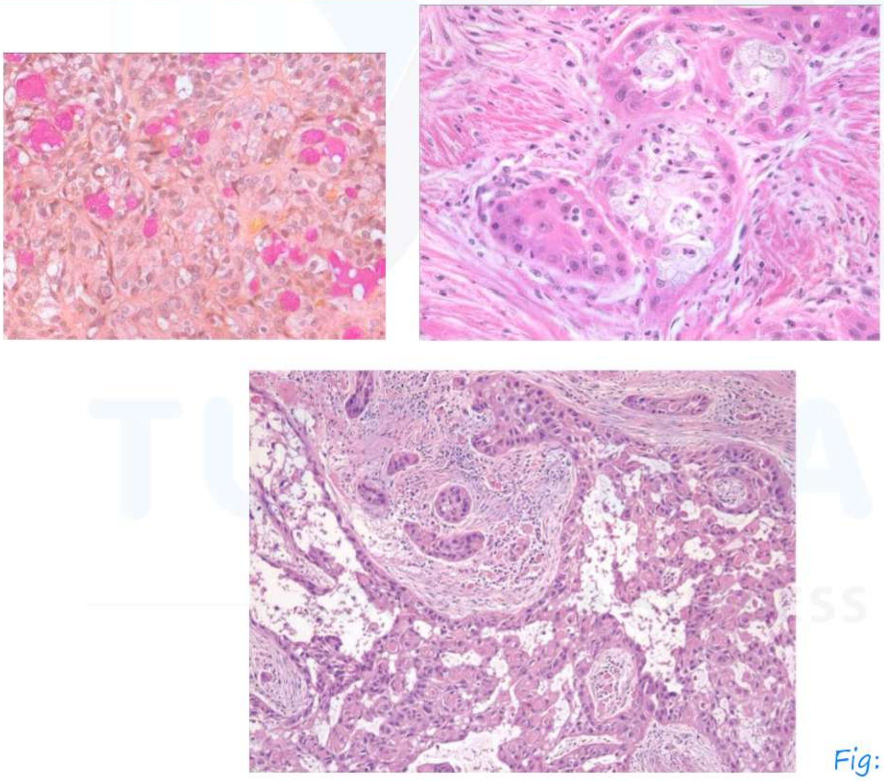


Fig: 9

## Acinic cell carcinoma 00:21:45

- Arises from secretory cells → resembles serous acini well defined tumors
- Men 20-30 years
- Encapsulated, round masses, under 3 cm

| Acinic cell Ca. | Normal serous salivary gland |
|---|---|
| • No lobular arrangement | • Lobular arrangement |
| • No | • Striated and intercalated ducts |

- 2nd most common malignant salivary gland tumor in children

| **IHC Markers** | |
|---|---|
| Benign | Malignant |
| • PA → PLAG 1<br>• Warthin's → Morphology | • Micro epidermoid → K167 increase<br>• Adenoid cystic → $^{\oplus}$ CD117$^{\oplus}$ and MyB<br>• Acinic cell |

DOT TUTORIALS LOGIN FOR SUCCESS

- Hyaline globules → Ad cc
- Chondromyxoid melting MEC → PA
- Myoepithelial cell identification → SIOO
  SMA
  P63
  P14
  Calponin
- Perineural invasion: Adenoid cystic carcinoma.

# HEAD AND NECK

Head & Neck

Oral cavity — Nose

↓

Ameloblastoma

↓

Tumor of odontogenic ep.

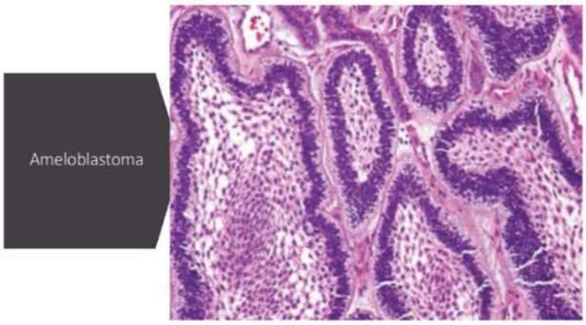
(Access in mandible / maxilla)

Unicystic — Multicystic

↓

Soap bubble appearance (X ray)

## Histopathology (HPE):

| Follicular pattern – more common | Plexiform |
|---|---|
| • Follicles with stellate reticulum<br>• Periphery of follicles – true palisading<br>• Reverse polarity<br><br> | • Cells form a network |

| | |
|---|---|
| • Craniopharyngioma of brain has wet keratin ameloblastoma does not<br>• Similar tumor occurs Li tibia – adamantinoma | |

## 1) Rhinoscleroma 00:05:25

Rhinoscleroma – Nose

↓

Klebsiella Rhinoscleromatous

Gram negative rods

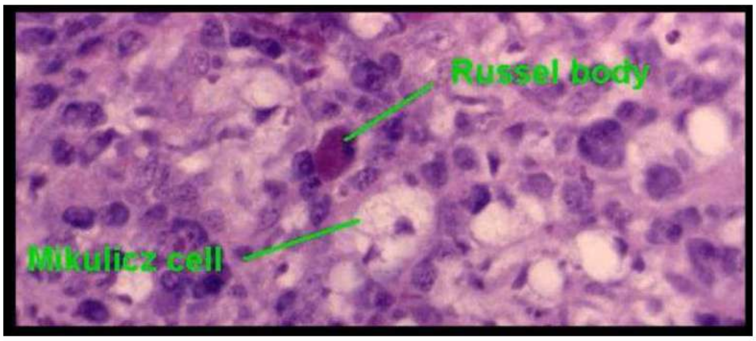
↓

- Macrophages of nose eat than up
- Plasma cells come → Make Igs in cytoplasm → Russel bodies

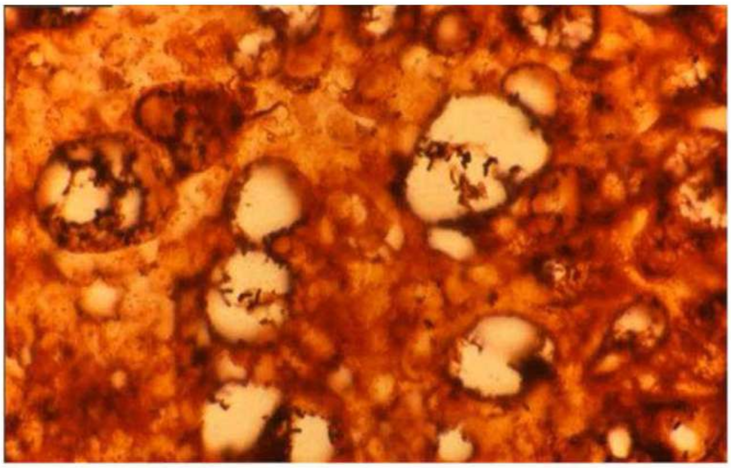
↓

- Macrophages become foamy – Mickuliz cells
- On PAS

  Warthin starry; Giemsa and stains rods can be seen in macrophages



Histopathology (magnified) Fig: 1



Warthin – Starry stain: Mikulicz cell

Fig: 2

## Stages of Rhinoscleroma 00:08:17

1) Catarrhal → carpenter glue
2) Atrophic → Crusting
3) Granulomatous (nodular) → macrophages → granulomas → nodules → Habra nose

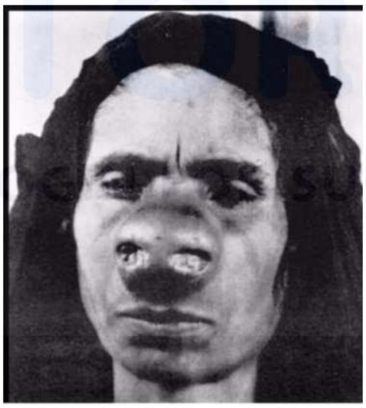


Fig: 3

4) cicatrical stage (Fibrosis) → TAPIR nose

Tapir
Hebra

Fig: 4

**Microscopy**

- Mickuliz cells
- Russel bodies

## 2) Lupus vulgaris 00:12:10

- Granulomatous lesion of nose
- Tuberculosis of nose and face
- Nodules have apple jelly appearance on diascopy

TUTORIALS LOGIN FOR SUCCESS

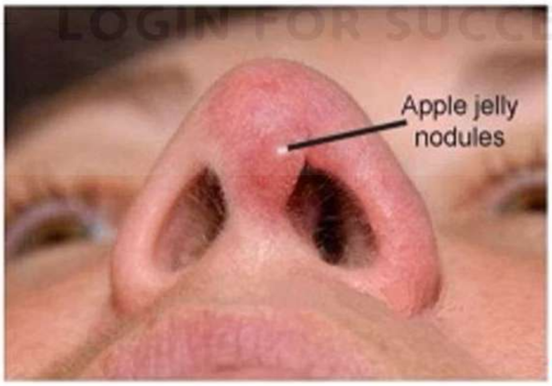
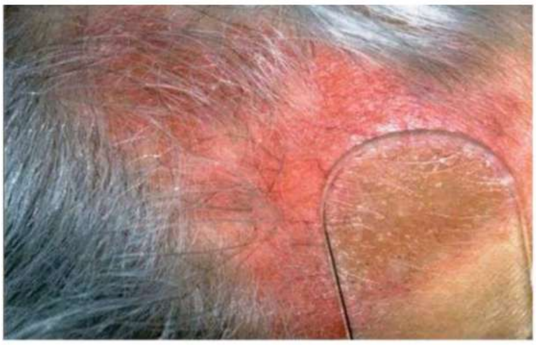

Apple jelly nodules

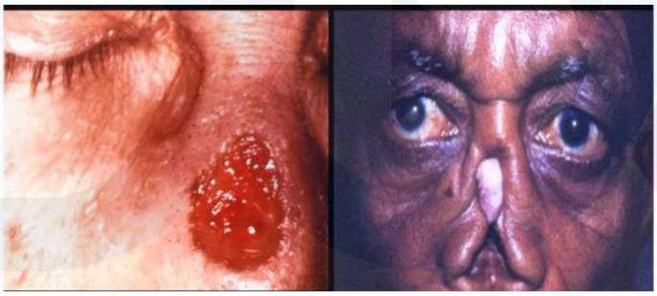
Fig: 5



Apply jelly nodule Fig: 6

- Can mimic a squamous cell carcinoma

## 3) Tertiary syphilis gumma 00:13:43

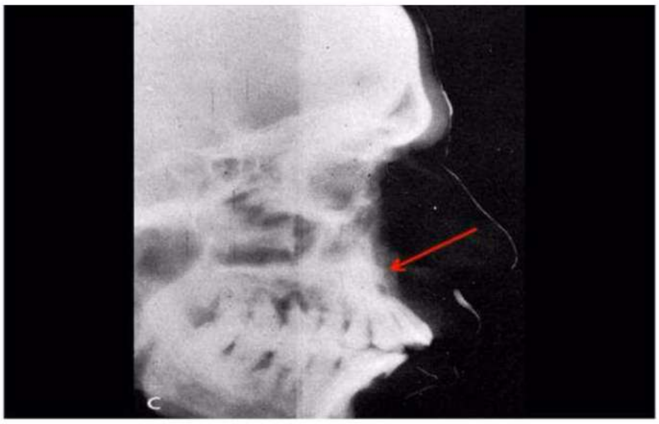


Tertiary syphilis gumma Fig: 7

**Investigations**

- Dark – ground illumination of nasal smear
- VDRL test
- RPR
- FTA – Ab test
- TPHA

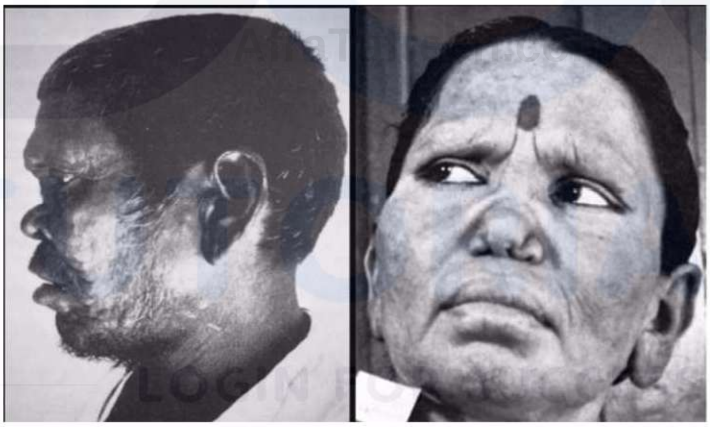
Erosion of anterior nasal spine



Erosion of anterior nasal spine Fig: 8

## 4) Saddle nose in leprosy 00:15:04

- Foam cells called Virchow cells
- Wadefite stain – globi of lepra bacilli (in lepromatous leprosy)



Saddle nose in leprosy Fig: 9

## 5) Rhinosporidosis 00:16:20

**Cause?**

- Bizarre fungus: obsolete theory
- Microcystis aeruginosa
- Aquatic parasite: Current theory
- Trophocyte is infective

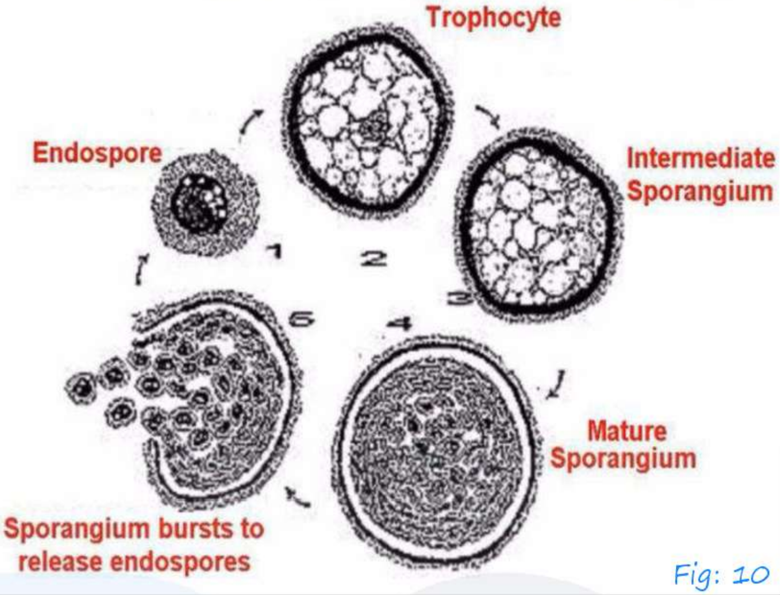
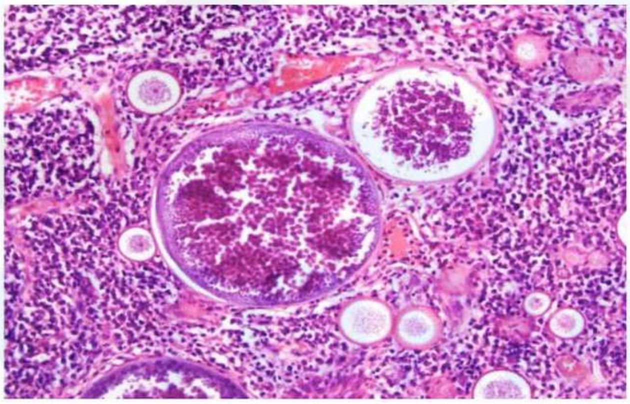
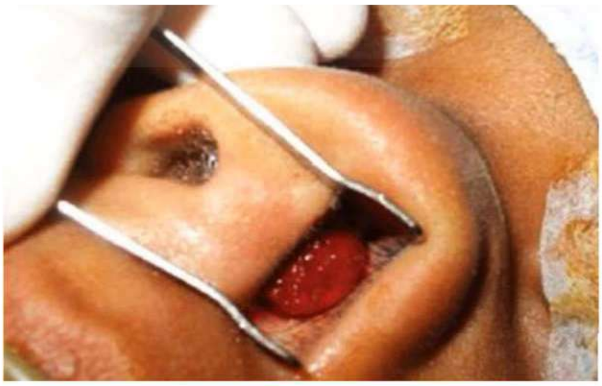

Trophocyte
Endospore
Intermediate Sporangium
Mature Sporangium
Sporangium bursts to release endospores
1
2
3
4
5

Fig: 10

- Sporangium is seen on microscopy full of endospores



Haematoxylin & Eosin stain Fig: 11



Bleeding nasal mass Fig: 12

- Gross – jelly like mass which bleeds on touch

- PAS positive
- GMS positive

## 6) Other Fungal lesions of nose 00:19:12

- Mucor mycosis:
  - Black crusting
  - Occurs in immune compromised, D.M> Patients
  - Angioinvasion
  - Aseptate fungi branch at 90°c
- Aspergilloma:
  - Aspergillus: dichotomous branching of hyphae
  - Septate

| Aspergillosis hyphae | Mucormycosis hyphae |
|---|---|
| Narrow | Broad |
| Septate | Non-septate |
| Branching at 45° | Branching at 90° |
| Dichotomous branching | Singular branching |

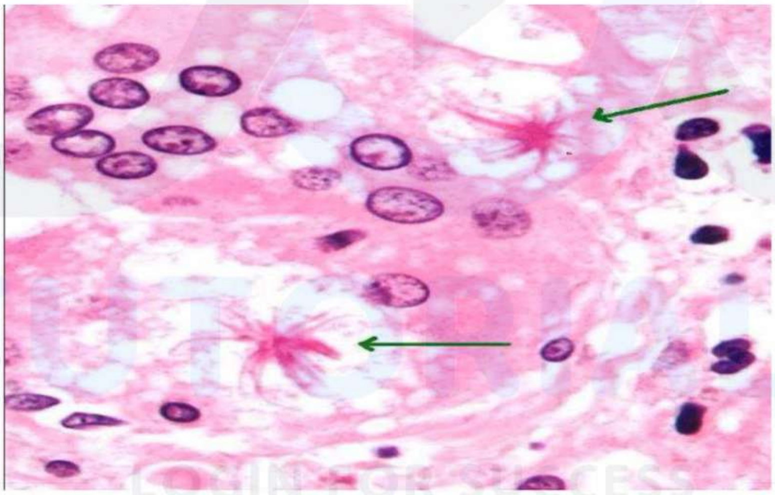
## 7) Sarcoidosis:

- Tip of nose becomes red and bullous – Lupus pernio
- Probe test – differentiate between lupus vulgaris and lupus pernio

## Probe test

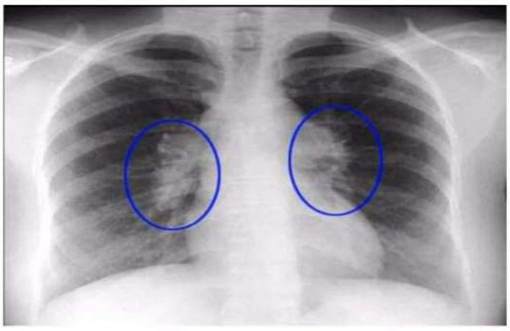
- Probing of nodular lesion to look for penetration.
- Negative in sarcoidosis: probe does not penetrate nodular swelling because of hard granulomas
- Positive in lupus vulgaris: probe penetrates up to soft granulation tissue in centre of nodule

- In sarcoidosis probe does not penetrate nodular swelling (negative)
- Sarcoidosis is a non-caseating granuloma
- Asteroid inclusion bodies seen



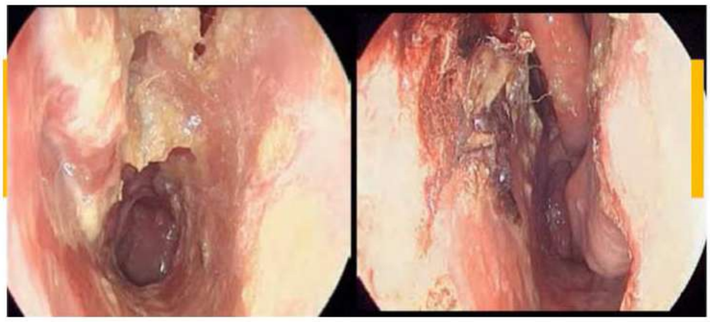
**Asteroid inclusion bodies** Fig: 13

- Har lymphadenopathy



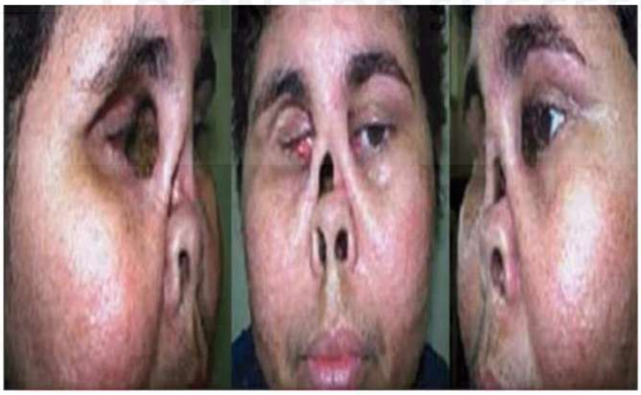
**Hilar lymphadenopathy** Fig: 14

## 8) Wegener's granulomatosis: 00:23:25

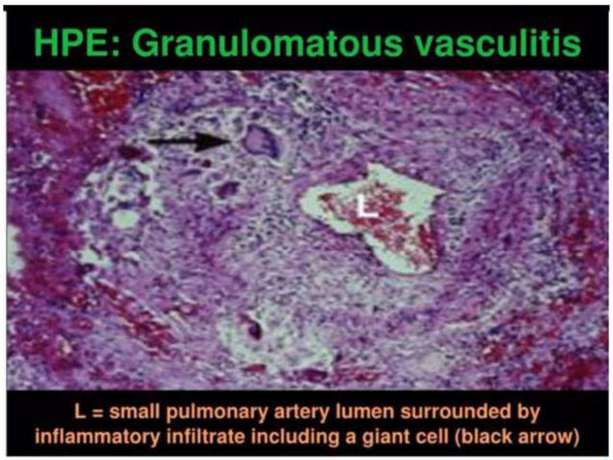


Crusting in nasal cavity Fig: 15

- Involves URT, LRT and kidney
- Starts with crusting can lead to septal perforation
- Lungs – canities
- Kidney – necrotizing GN
- Limited Wegener's (strawberry gems) – Respiratory tract involved, kidney spared
- Microscopically: Granulomatous vasculitis
- C – ANCA by indirect immunofluorescence – confirmatory



**Destruction of orbit & nose** Fig: 16



HPE: Granulomatous vasculitis

L = small pulmonary artery lumen surrounded by inflammatory infiltrate including a giant cell (black arrow)

Fig: 17

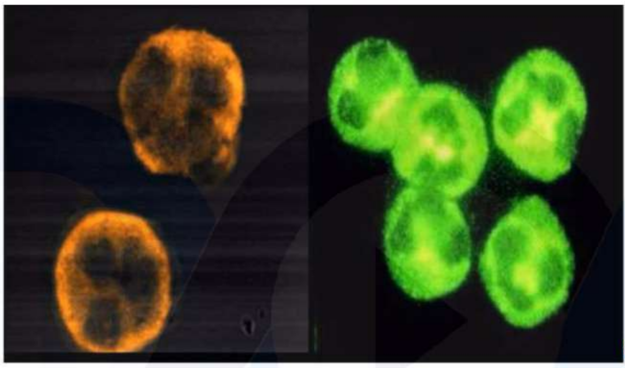


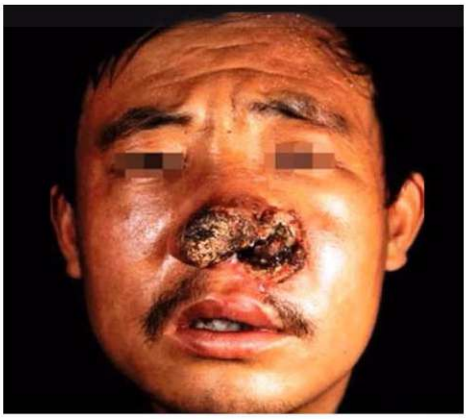
Fig: 18

C – ANCA by indirect immune-fluorescence

## 9) NK/ T cell lymphoma 00:25:10

- Stewarts granuloma
- Lethal midline granuloma
- Mid face mutilation

TUTORIALS LOGIN FOR SUCCESS



Mid-face mutilation

Fig: 19

- Malignant cells will be positive for (1) 16 and (1) 56

## Differentiation between Wegener's and sinonasal lymphoma 00:23:25

| Wegener's Granuloma | Sinonasal Lymphoma |
|---|---|
| Bilateral involvement | Unilateral involvement |
| Slowly progressive | Rapidly progressive |
| Diffuse ulceration | Focal ulceration |
| Extensive crusting | Moderate crusting |
| Absence of gross destruction of midface | Gross destruction of mid-face present |
| Pulmonary & renal involvement present | No pulmonary or renal involvement |

| Investigation | Wegener's Granuloma | Sinonasal Lymphoma |
|---|---|---|
| Vasculitis | Present | Absent |
| Granulomas | Present | Absent |
| Giant cell | Present | Absent |
| Atypical T lymphocytes | Absent | Present |
| Angio-invasion | Absent | Present |
| C-ANCA titre | Raised | Not raised |

## 10) Churg Strauss syndrome 00:27:50

- Allergic granulomatosis
- Present with nasal polyps + bronchial asthma
- Chest x ray- Pulmonary lesions
- HPE of polyp: Necrotizing granulomas with abundant eosinophils without vasculitis

## 11) Leishmaniasis 00:29:00

- Nasal disease – espundia
- LD bodies seen on microscopy, nucleus with kinetoplast should be seen

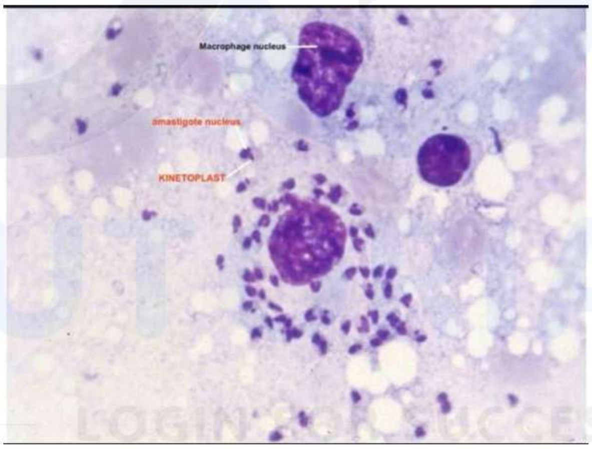

Macrophage nucleus
amastigote nucleus
KINETOPLAST

Fig: 20

# HEAD AND NECK

Head & Neck

Oral cavity | Nose

↓

Ameloblastoma

↓

Tumor of odontogenic ep.

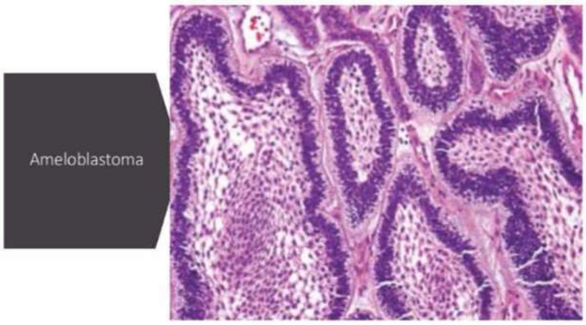
(Access in mandible / maxilla)

Unicystic | Multicystic

↓

Soap bubble appearance (X ray)

**Histopathology (HPE):**

| Follicular pattern – more common | Plexiform |
|---|---|
| • Follicles with stellate reticulum<br>• Periphery of follicles – true palisading<br>• Reverse polarity<br> | • Cells form a network |

| | |
|---|---|
| • Craniopharyngioma of brain has wet keratin ameloblastoma does not<br>• Similar tumor occurs Li tibia – adamantinoma | |

## 1) Rhinoscleroma 00:05:25

Rhinoscleroma – Nose

↓

Klebsiella Rhinoscleromatous

Gram negative rods

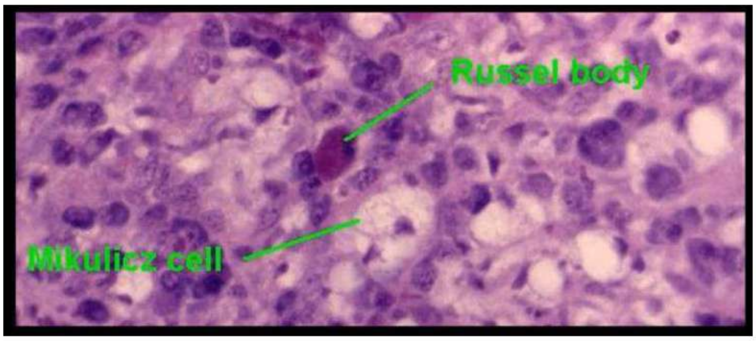
↓

- Macrophages of nose eat than up
- Plasma cells come → Make Igs in cytoplasm → Russel bodies

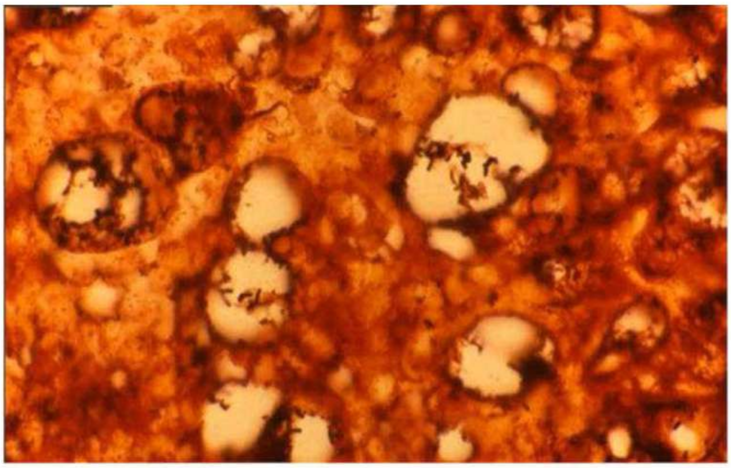
↓

- Macrophages become foamy – Mickuliz cells
- On PAS

  Warthin starry; Giemsa and stains rods can be seen in macrophages



Histopathology (magnified) Fig: 1



Warthin – Starry stain: Mikulicz cell

Fig: 2

## Stages of Rhinoscleroma 00:08:17

1) Catarrhal → carpenter glue
2) Atrophic → Crusting
3) Granulomatous (nodular) → macrophages → granulomas → nodules → Habra nose

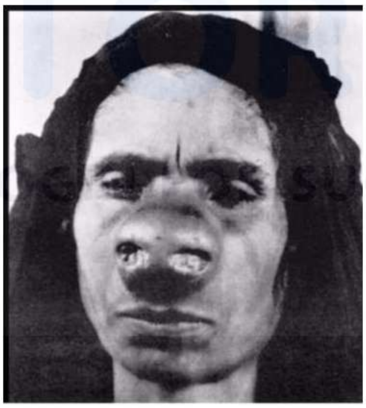


Fig: 3

4) cicatrical stage (Fibrosis) → TAPIR nose

Tapir
Hebra

Fig: 4

**Microscopy**

- Mickuliz cells
- Russel bodies

## 2) Lupus vulgaris 00:12:10

- Granulomatous lesion of nose
- Tuberculosis of nose and face
- Nodules have apple jelly appearance on diascopy

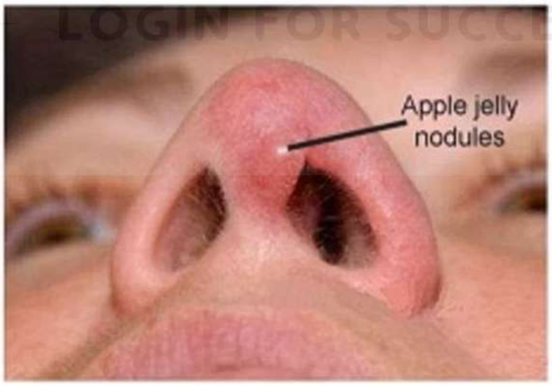
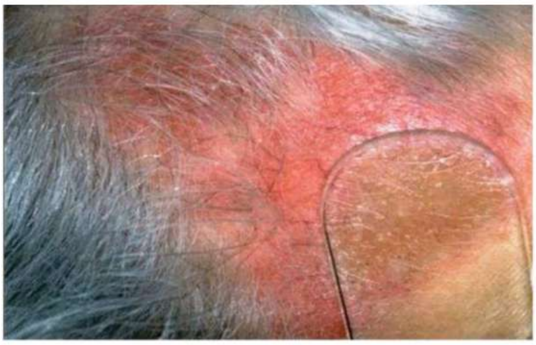

Apple jelly
nodules

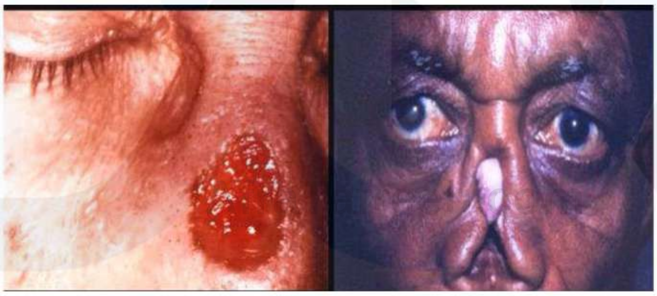
Fig: 5



Apply jelly nodule Fig: 6

- Can mimic a squamous cell carcinoma

## 3) Tertiary syphilis gumma 00:13:43

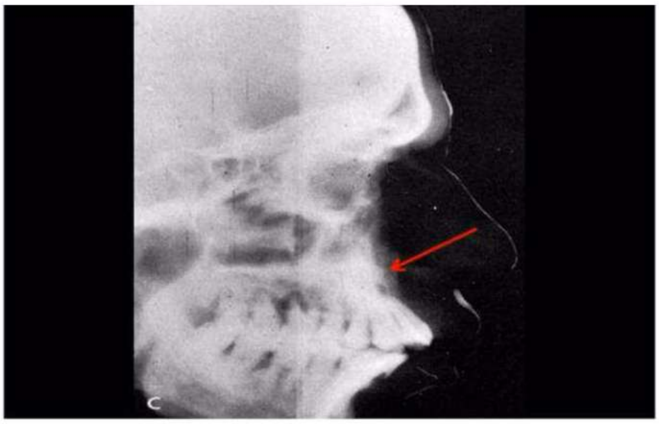


Tertiary syphilis gumma Fig: 7

**Investigations**

- Dark – ground illumination of nasal smear
- VDRL test
- RPR
- FTA – Ab test
- TPHA

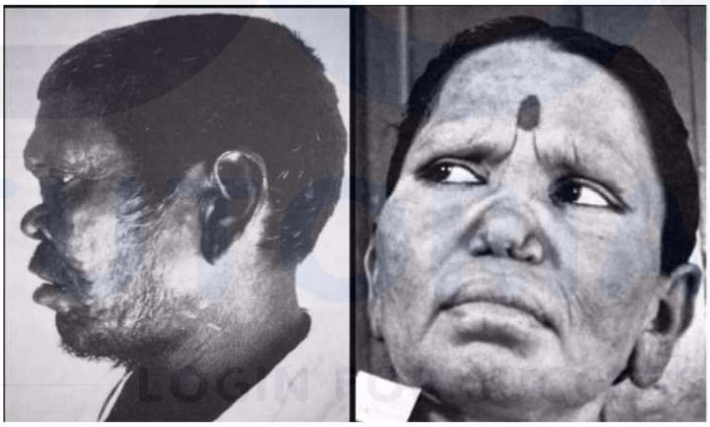
Erosion of anterior nasal spine



Erosion of anterior nasal spine Fig: 8

## 4) Saddle nose in leprosy 00:15:04

- Foam cells called Virchow cells
- Wadefite stain – globi of lepra bacilli (in lepromatous leprosy)



Saddle nose in leprosy Fig: 9

## 5) Rhinosporidosis 00:16:20

**Cause?**

- Bizarre fungus: obsolete theory
- Microcystis aeruginosa
- Aquatic parasite: Current theory
- Trophocyte is infective

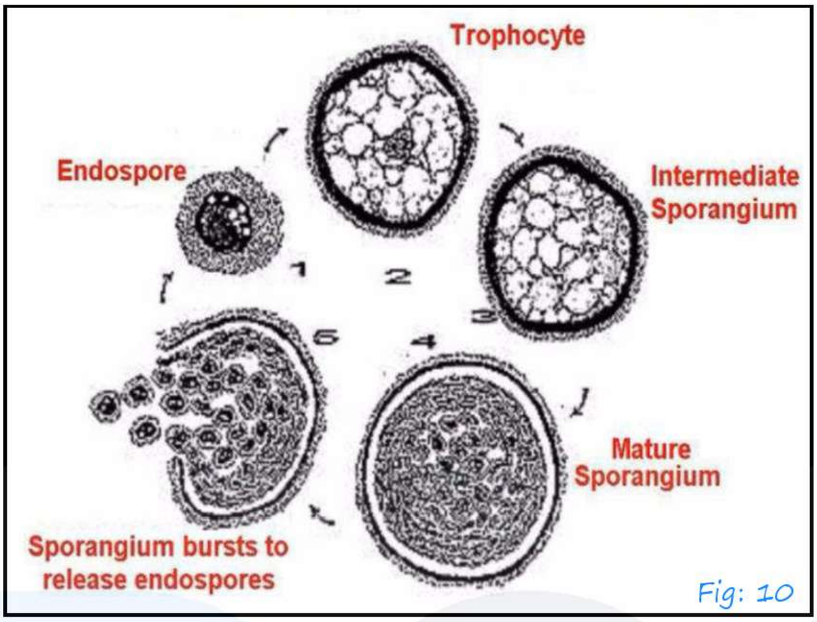
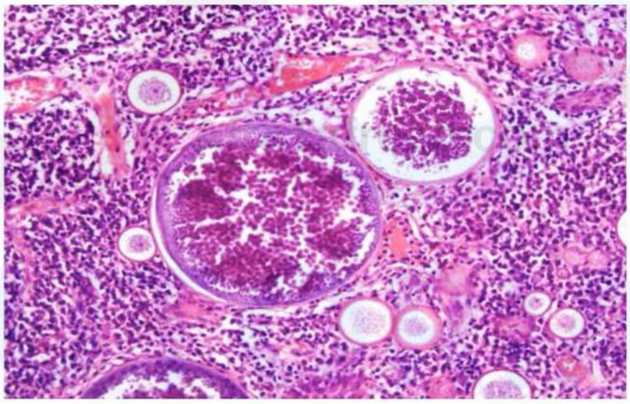
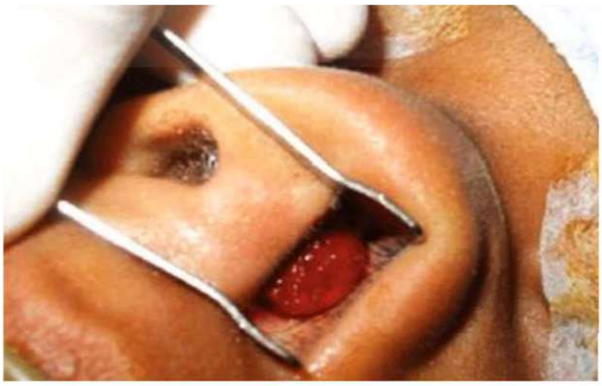

Trophocyte
Endospore
Intermediate Sporangium
1
2
3
4
5
Mature Sporangium
Sporangium bursts to release endospores

Fig: 10

- Sporangium is seen on microscopy full of endospores



Haematoxylin & Eosin stain Fig: 11



Bleeding nasal mass Fig: 12

- Gross – jelly like mass which bleeds on touch

- PAS positive
- GMS positive

## 6) Other Fungal lesions of nose 00:19:12

- Mucor mycosis:
  - Black crusting
  - Occurs in immune compromised, D.M> Patients
  - Angioinvasion
  - Aseptate fungi branch at 90°c
- Aspergilloma:
  - Aspergillus: dichotomous branching of hyphae
  - Septate

| Aspergillosis hyphae | Mucormycosis hyphae |
|---|---|
| Narrow | Broad |
| Septate | Non-septate |
| Branching at 45° | Branching at 90° |
| Dichotomous branching | Singular branching |

TUTORIALS LOGIN FOR SUCCESS

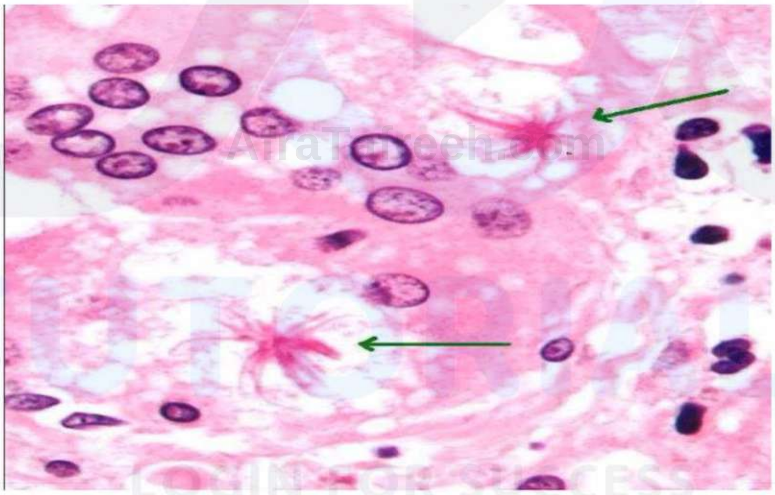
## 7) Sarcoidosis:

- Tip of nose becomes red and bullous – Lupus pernio
- Probe test – differentiate between lupus vulgaris and lupus pernio

### Probe test

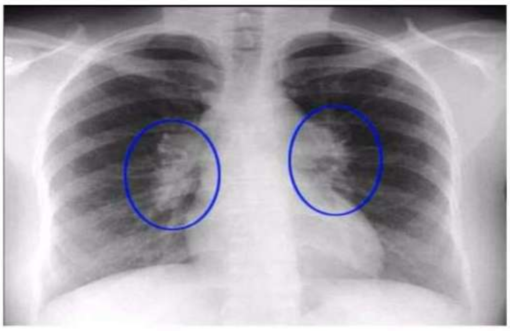
- Probing of nodular lesion to look for penetration.
- Negative in sarcoidosis: probe does not penetrate nodular swelling because of hard granulomas
- Positive in lupus vulgaris: probe penetrates up to soft granulation tissue in centre of nodule

- In sarcoidosis probe does not penetrate nodular swelling (negative)
- Sarcoidosis is a non-caseating granuloma
- Asteroid inclusion bodies seen



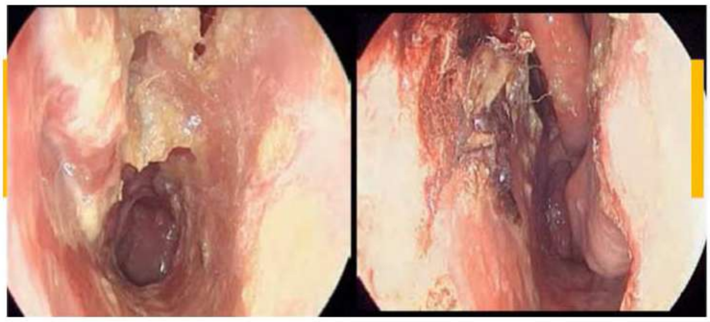
**Asteroid inclusion bodies** Fig: 13

- Har lymphadenopathy



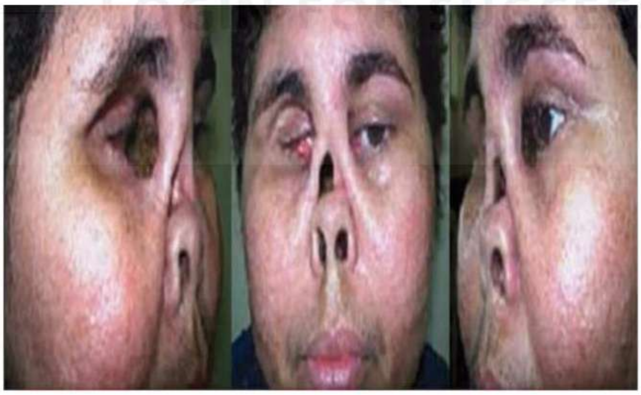
**Hilar lymphadenopathy** Fig: 14

## 8) Wegener's granulomatosis: 00:23:25

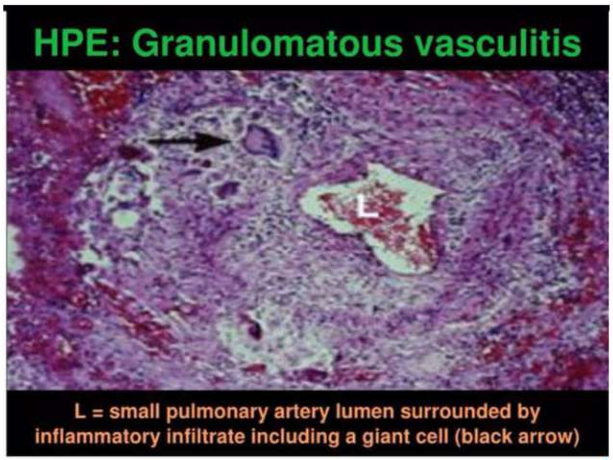


Crusting in nasal cavity Fig: 15

- Involves URT, LRT and kidney
- Starts with crusting can lead to septal perforation
- Lungs – canities
- Kidney – necrotizing GN
- Limited Wegener's (strawberry gems) – Respiratory tract involved, kidney spared
- Microscopically: Granulomatous vasculitis
- C – ANCA by indirect immunofluorescence – confirmatory



**Destruction of orbit & nose** Fig: 16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L
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Fig: 17

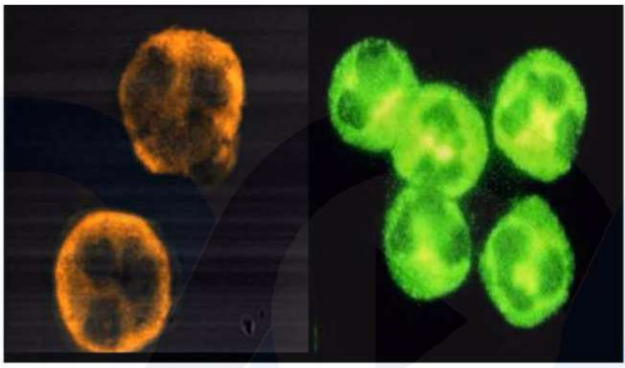

Fig: 18

C – ANCA by indirect immune-fluorescence

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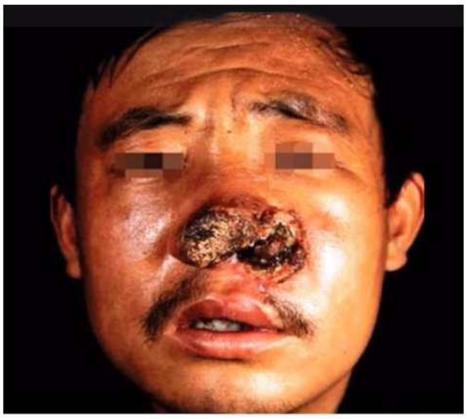

Mid-face mutilation

Fig: 19

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TUTORIALS LOGIN FOR SUCCESS

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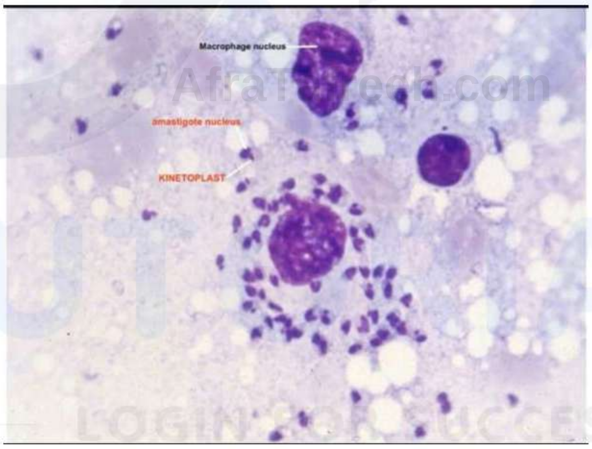
Macrophage nucleus
amastigote nucleus
KINETOPLAST
AfraTafreeh.com

Fig: 20

TUTORIALS LOGIN FOR SUCCESS

# CLASSIFICATION OF CYSTIC LESIONS OF PANCREAS

## Cystic lesions of pancreas 00:00:20

No neoplastic lesion

Congenital cysts → AD-PCKD

VHL (Vons Hippel-Lindau)

Neoplastic lesion

SIZE

- Microcyst
  Serous tumors
  tumors

Macrocysts
mucinous

(Always benign)

Communication pancreatic duct?

Yes

Intra ductal
Papillary mucinous
Neoplasm (IPMN)

No

mucinous

Pre-cancerous

- Grandmother – senile age group – serous more common
  ♂♀ – IPMN – No predilection for sec
- Mother – middle age – mucinous
- Daughter – young age group – SPEN (females) - solid – papillary – neoplasm pseudo

## Serous tumors 00:10:00

- More common elderly females
- Associated with VHL mutation
- No communication with pancreatic duet
- Microcystic with central scar
- Calcification microscopy: lined by flattered cuboidal epithelium
- Always benign
- On radiology: bunch of grapes appearance

## Mucinous tumors 00:12:40

- Most common in female middle ate
- KRAS mutation
- Pre-cancerous but when they turn cancerous & invasive, they have - P53 mutation
  SMAD
- Macrocystis
- No communication with pancreatic duct
- Microscopy: lined by columnar ep filled with mucin devise ovarian stroma → negative for ER, PR & inhibitor

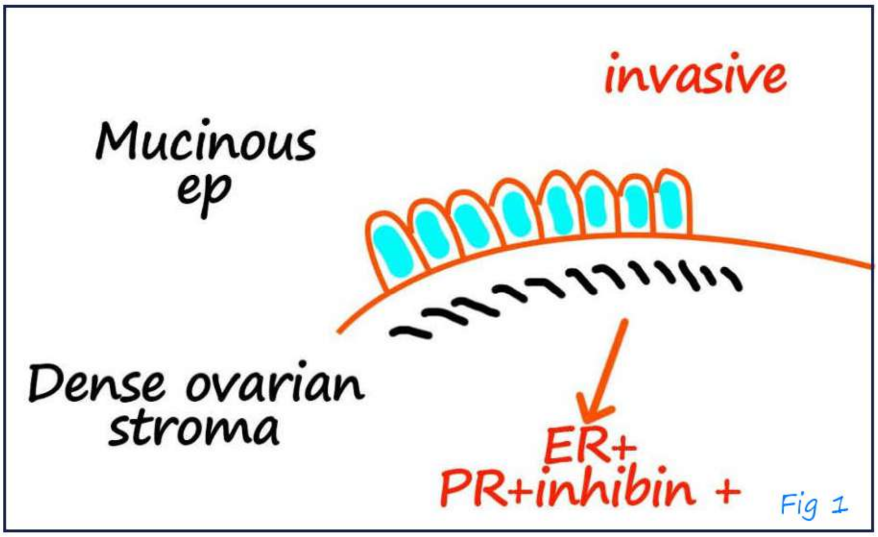
invasive
Mucinous ep
Dense ovarian stroma
ER+
PR+inhibin +

Fig 1

| Cyst aspirate analysis | Viscosity | Amylase | CEA |
|---|---|---|---|
| Pseudocyst | Decrease | Increase | Normal |
| Serous cystadenoma | Decrease | Normal | Normal |
| Mucinous cystadenoma | Increase | Increase | Increase |
| IPMN | Increase | Increase | Increase |

## Pseudocysts 00:17:40

- Common abdominal masses in surgery
- Due to trauma & pancreatitis
- Does not have a ep lining
- Pancreatitis → hemorrhage

  (Acute exacerbation ↓

  Necrosis → granulation tissue

## Pancreatic adenocarcinoma 00:19:28

- Can arise from IPMN & mucinous tumors
- Risk factors: smocking
  Alcohol
  DM
- Mutation: KRAS (most common)
  P53 females
  SAMD shortening
  P16 occurs early

  * BRCA2 (also seen in male breast)
  * STK II (PTS)
  ANPCC
- Morphology: glands in stroma
  - Stroma is desmoplastic

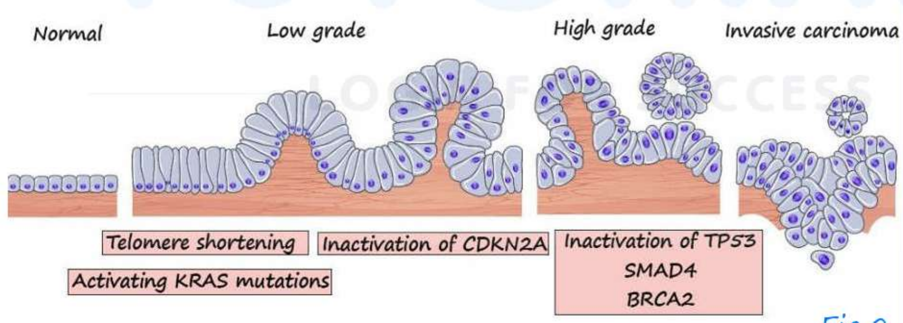
Normal
Low grade
High grade
Invasive carcinoma
Telomere shortening
Inactivation of CDKN2A
Inactivation of TP53
SMAD4
BRCA2
Activating KRAS mutations

Fig 2

- Mutation is hereditary pancreatitis PRSS1, SPINK 1
- B- catenin → also called CTNNB1

| Inherited Predisposition to Pancreatic Cancer | | | |
|---|---|---|---|
| **Disorder** | **Gene** | **Increased Risk of Pancreatic Cancer (Fold)** | **Risk of Pancreatic Cancer by Age 70 (%)** |
| Peutz-Jeghers syndrome | STKII | 130 | 30-60 |
| Hereditary pancreatitis | PRSSI,<br>SPINKI | 50-80 | 25-40 |
| Familial atypical multiple-mole melanoma syndrome | CDKNZA | 20-35 | 10-17 |
| Strong family history (3 or more relatives with pancreatic cancer) | Unknown | 14-32 | 8-16 |
| Hereditary breast and ovarian cancer | Multiple. including BRCA BRCA2 | 4-10 | 5 |

| | | | |
|---|---|---|---|
| | PALB2,<br>ATM | | |
| Hereditary non-polyposis colorectal cancer | Multiple, including MLHI, MSH2, PMS2 | 8-10 | 4 |

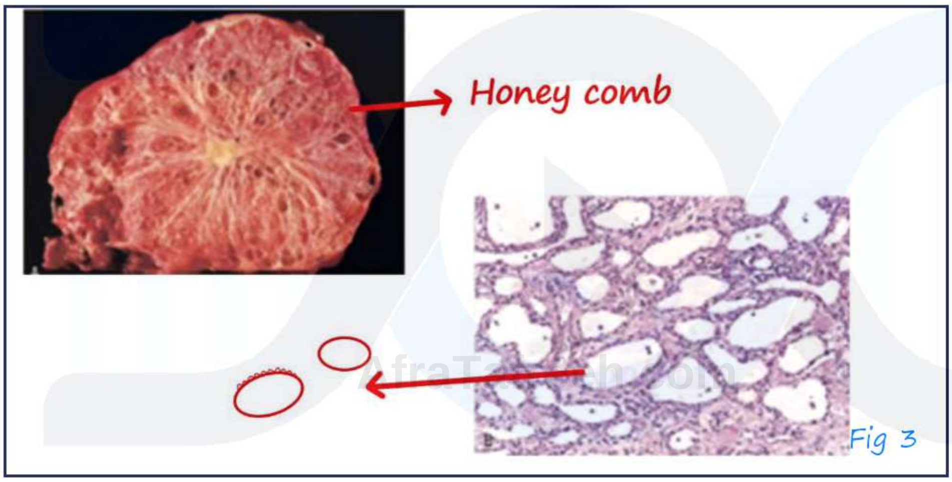

Fig 3

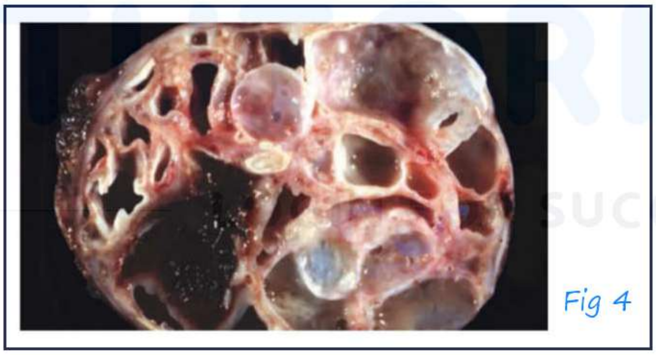

Fig 4

## Epigenetic change in pancreatic tumors

00:28:25

Mucinous cystic neoplasm

Ovarian stroma: ER,PR,inhibin+

KRAS: 5 percent

Invasive: p53 and SMAD4

- RNF43 → E3 ubiquitin ligase

  ↓

  Regulates WNT pathway
- Del of RNF43 is seen in mucinous tumors of pancreas & colorectal cancers

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## IPMN

00:29:20

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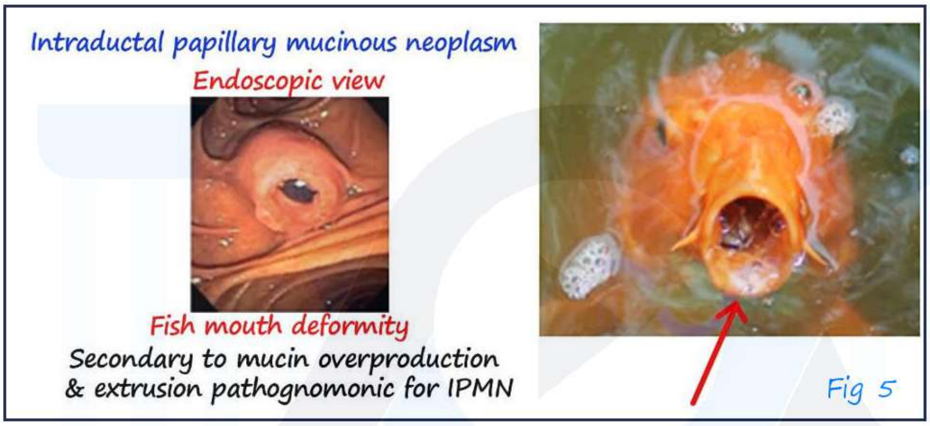

Intraductal papillary mucinous neoplasm

Endoscopic view

Fish mouth deformity

Secondary to mucin overproduction & extrusion pathognomonic for IPMN

Fig 5

- Fish mouth deformity on endoscopy

- Secondary to mucin overproduction
- Pre-cancerous
- Connection to duct

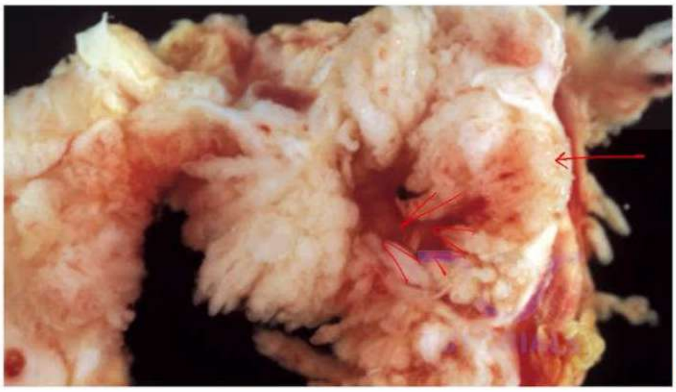

Fig 6

- GNAS mutation

**Malignant potential:**

- IPMN > mucinous> serous > pseudocysts

## Solid pseudopapillary neoplasm (SPEN) 00:31:55

- Young females
- Occurs in body tail of pancreas
- Pseudopapillary projections (no fibrovascular core)
- B-catenin mutation is seen in almost all cases
- Hamoud or Frantz tumor

# ABO, RH, KELL LEWIS, DUFFY BLOOD GROUPS AND METHODS OF BLOOD GROUPING

Blood bank

Blood groups

i. ABO Blood group

ii. Rh blood group

iii. Other group (Rare)

## ABO Blood group 00:01:42

- ABO antigen made up of carbohydrate 1 sugars
- These antigens are widespread and present on the membrane of various cells like RBC, WBC, Platelets
- Its is also found is secretion except is cerebrospinal fluid
- It is also found in other organs like cervical cells, gastro intestinal cells,
- Naturally occurring antibodies are found in the body against ABO antigen
- These antigens are IgM some are IgG also

Acute Hemolytic Reaction → Transfusion of mismatched blood leads to intravascular hemolysis due to IGM antibodies leading to hemoglobinuria.

- Molecular Genetics of ABO system
- Chromosome 19 -it codes for enzymes L- Fucosyl transferase
- This enzyme adds fucose. Fucose attach to oligo saccharide of cells

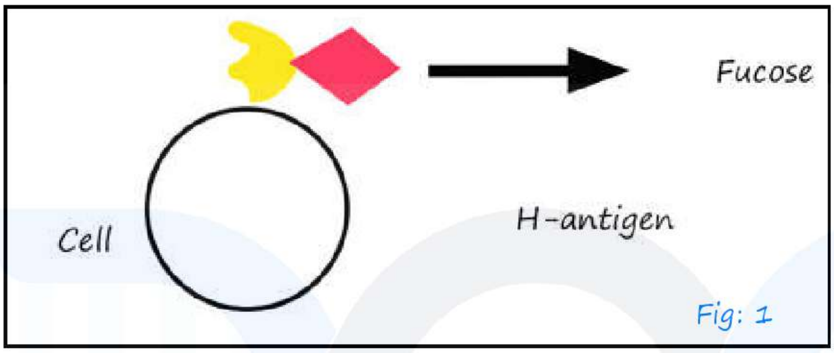
Fucose
Cell
H-antigen

Fig: 1

- H antigen is the first to be formed

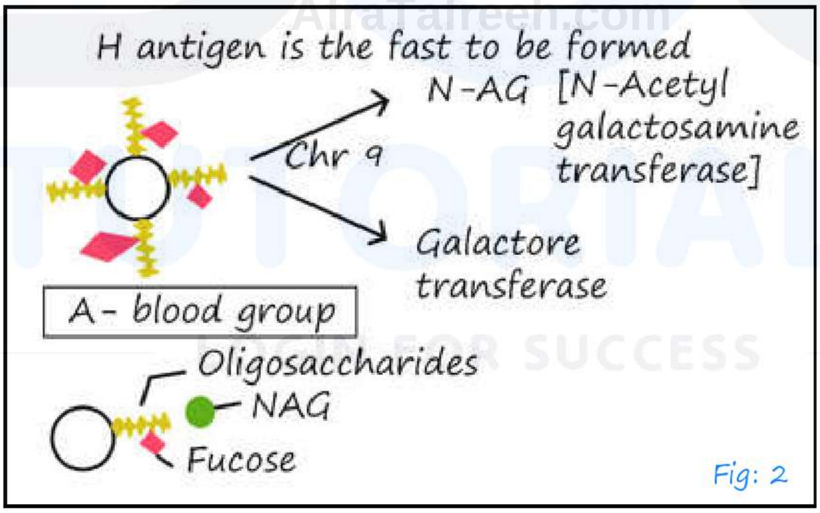
H antigen is the fast to be formed
N-AG [N-Acetyl galactosamine transferase]
Chr 9
Galactore transferase
A- blood group
Oligosaccharides
NAG
Fucose

Fig: 2

- A Antigen + H antigen + Anti B in plasma

## B Blood Group

B blood group contains

- B antigen + H antigen + Anti A antibody in plasma

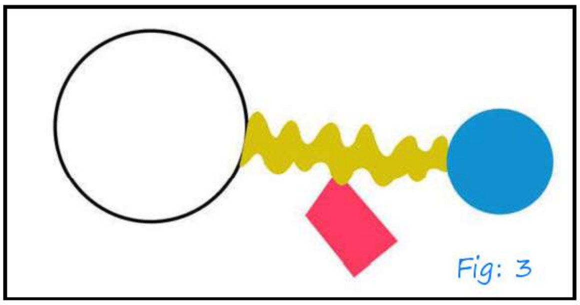

Fig: 3

## AB Blood Group

AB blood group contain

- A antigen B antigen< H antigen No antibody Plasma

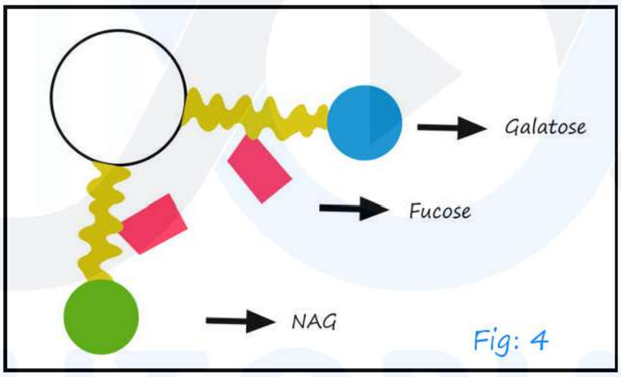

Fig: 4

## O Blood group

- O blood group contains H antigen, Anti A and B is plasma
- Maximum 'H' antigen present in o blood group
- Least 'H' antigen substance / present in AB blood group
- Blood group shows codominance inheritance
- 'Se' gene controls if H antigen will be secreted as 'H antigen

- AB blood group is a universal recipient since it has no antibodies
- O Blood group is universal donor since it how no antigen

## Bombay Blood Group 00:28:20

- CH-19 does not produce L- fructosyl transferase Hence No fucose, No A antigen, No H antigen. The plasma contains Anti A, Anti H, Anti B antibodies
- Bombay Blood group induvial associate with leucocyte adhesion Defect-2

### Genotypic finding of Blood group

| Phenotype | Genotype |
|---|---|
| A Blood Group | AA<br>AH |
| B Blood Group | BB<br>BH |
| O Blood Group | HH |
| AB Blood group | AB Bombay Blood group -hh |

### Rh Blood Group

- These are proteins
- It is usually present on red Blood cells

- These proteins are called 12 PASS PROTEINS ( 6 loops outside & 6 loops inside

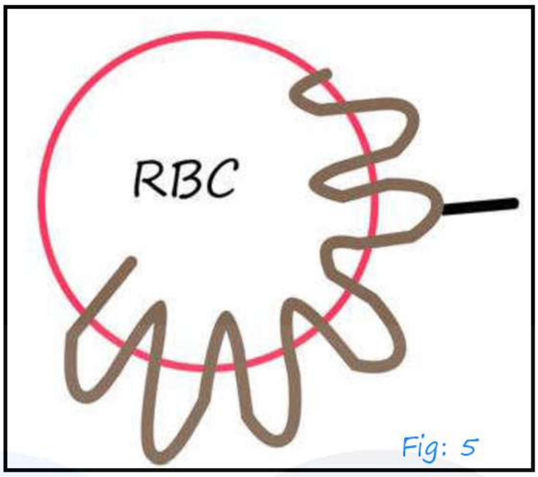

Fig: 5

## Molecular Genetics

Chr 1→ 2 gens i. Rh D antigen → codes for D

ii. Rh, C.E antigen → codes for C, c, E, e

Rh antigen is made up of

| | |
|---|---|
| D antigen | C |
| - most common | c |
| - most common | E |
| | E |

- Antigen to Rh antigen are NOT present naturally
- Antibodies to Rh antigen are produced when the individual are sensitized & IgG antibodies are then produced
- Sensitization occurs due to transfusion, vertical transmission from mother

- Rh Hemolytic Disease of new born is more common & more severe than ABO hemolytic disease

High yield Box

Chr 1 – Rh Antigen
Chr 9 – AB antigen
Chr 19 – H antigen

## Others

### a. Kell antigen

- Present on Red Blood cells
- After Rh antigen these are next immunogenic

ML Leod phenotype

- Individual having no kell antigen
- These individuals have Acanthocytes (RBC cells having irregular spikes) also seen in liver disorders
- Also, more prone to chronic granulomatous disease
- Also, more prone to muscular d dysfunction

### b. Duffy Antigen

- It is present on RBC's
- It coded by DARC gene (Duffy Antigen Receptor for cytokines)
- DARC is receptor for IL -8 , MCP
- Protect against Plasmodium vivax and plasmodium Knowlesi

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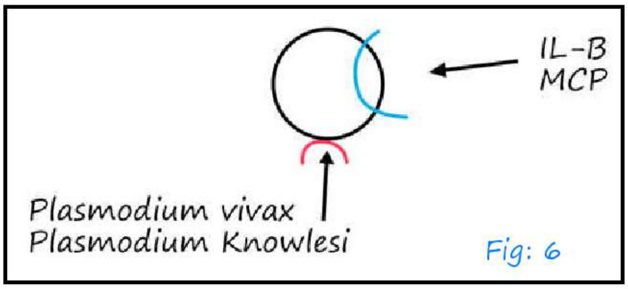

IL-B
MCP
Plasmodium vivax
Plasmodium Knowlesi

Fig: 6

- Recent Outbreak of malaria in Malaysia due to Plasmodium knowlesi

## c. Lewis Antigen

- It is not produced by RBC
- It is secreted Antigen. It is secreted by epithelial cells
- These Antigens are Absorbed onto the surface of RBC's

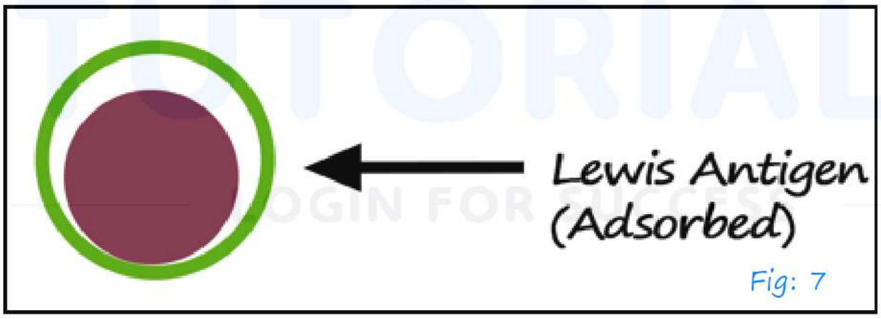

Lewis Antigen
(Adsorbed)

Fig: 7

- Lewis Antigen is a 12 PASS Antigen

Rh Null: individuals having No C, D, E, Antigen

Rh positive: individuals FD +ve

Rh Negative: individual D -ve

Weak D: less No of D antigen on RbC's

Weak D as a Donor → considered Rh+

Weak D as a Recipient → considered Rh-

Partial D: Partial missing of Rh determinants.

# TEST FOR BLOOD GROUPING

## Blood Group

### Testing of Blood Group

i. Slide or Tiles testing

ii. Tube

iii. Gel Technique or column Agglutination

## i. Slide testing/Tiles testing 00:01:12

- Always Antisera are added first

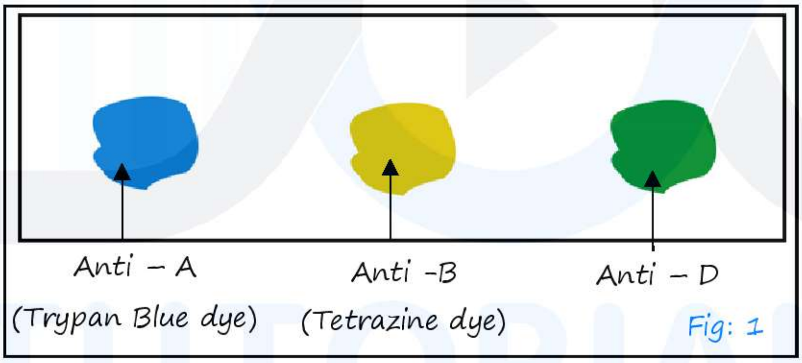

Anti – A
(Trypan Blue dye)
Anti -B
(Tetrazine dye)
Anti – D

Fig: 1

### Steps

i. Blood taken from individual

ii. Blood centrifuged

iii. 30-40% suspensions of cells created

iv. Cells are added to antisera

Cells to Antisera Ratio 1:1

Blood Group A+

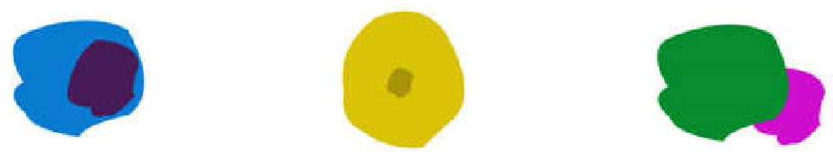
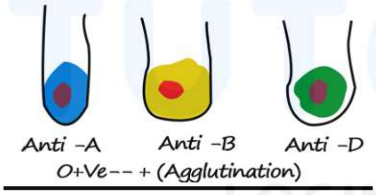
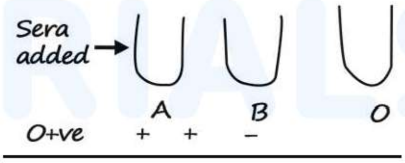


Fig: 2

- Clumping present in Anti A and Anti D
- This method wad used earlier
- Now, forward and reverse grouping is performed

## ii. Tube testing 00:15:40

| Forward grouping | **Reverse grouping** |
|---|---|
| - This is done with Red Blood cells<br><br> Anti -A<br>Anti -B<br>Anti -D<br>O+Ve-- + (Agglutination)<br>- Bombay Blood group - - +<br>- Forward and Reverse Grouping is done in Tubes | - This is done to detect sera<br><br> Sera added<br>A<br>B<br>O<br>O+ve<br>+ +<br>–<br>- (O+ ve has anti A and anti B in Sera, hence agglutination seen) + ++<br>- (Bombay Blood group has anti A, Anti B & Anti H antibody) |

### Reverse grouping

- 50% suspension of cells is taken and added to anti sera
- The 5% suspension of cells tomato colored
- Cells: sera= 2:1

## iii. Gel Technique 00:16:50

- Gel are preloaded with antisera
- Cells are added to Gel
- It cells agglutinate, they are at top of they do not agglutinate they move down

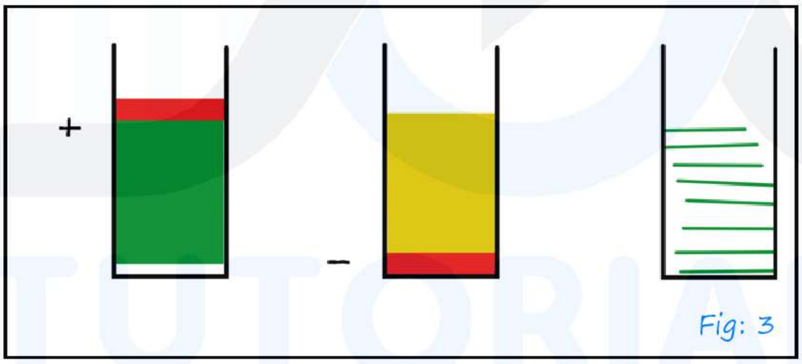


Fig: 3

# BLOOD BAGS

## Donor criteria 00:00:34

- Hb> 12.5 gm/dl
- Weight > 45kg
- Normotensive, healthy individual

### Donors

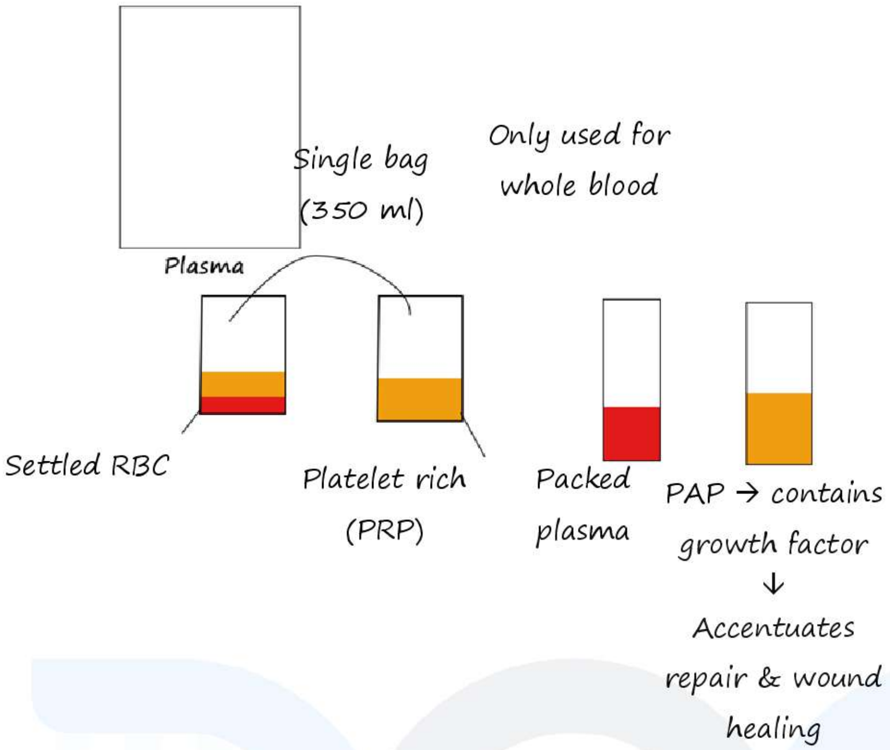
- Voluntary blood donors – best type
- Replacement blood donors
- Paid donor -not preferred banned in India
- Autologous donors – people with rare blood groups donating blood for themselves
- Apheresis donors – Blood is separated into derived complements & the rest of blood us transferred back to the donor

### Weight criteria for blood donation

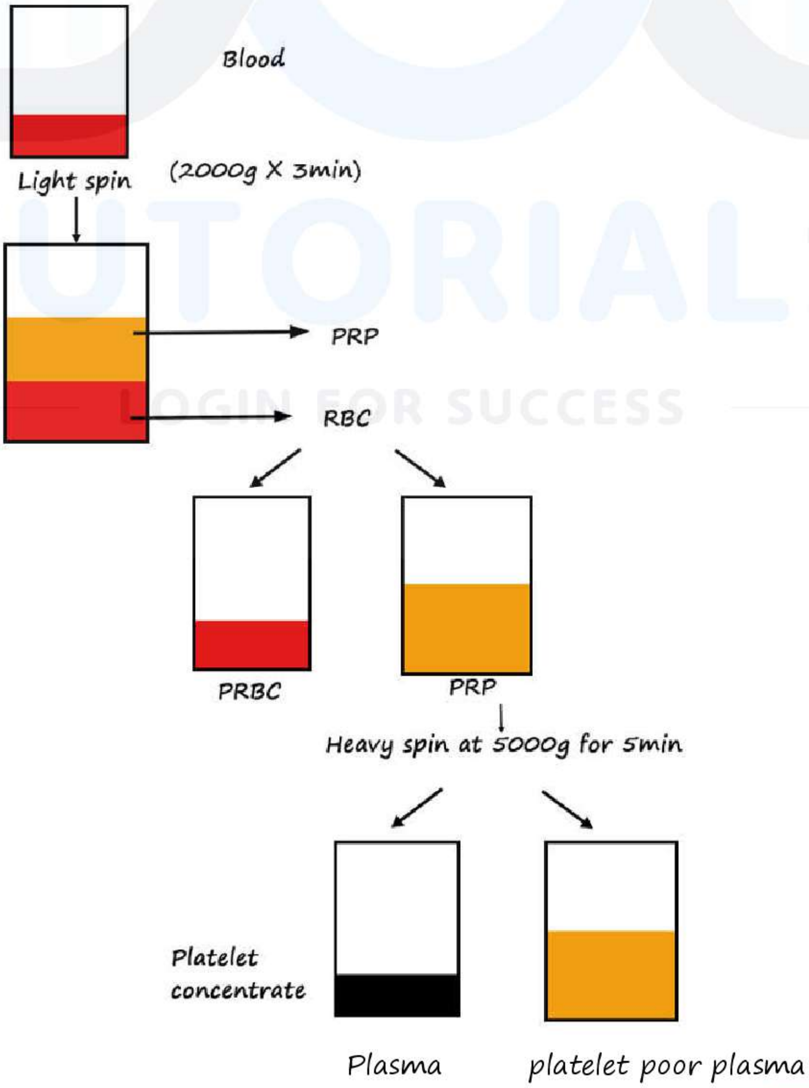
- If donors' weight > 45kg but < 55 kg = 350 ml blood
- > 55kg = 450 ml

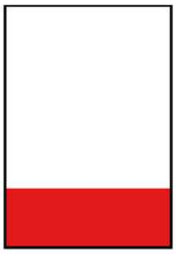
### Blood bags

- Single bag only for used for whole blood (350 ml)


Single bag
(350 ml)
Only used for
whole blood
Plasma
Settled RBC
Platelet rich
(PRP)
Packed
plasma
PAP → contains
growth factor
↓
Accentuates
repair & wound
healing

## Triple bags

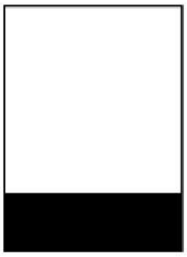

Blood
Light spin
(2000g X 3min)
PRP
RBC
PRBC
PRP
Heavy spin at 5000g for 5min
Platelet
concentrate
Plasma
platelet poor plasma



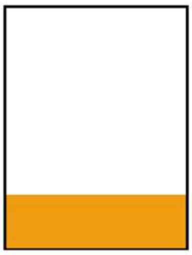
PRBC

↓

- Stored at 2-6 °
- ABO & Rh matched



PC



platelet poor plasma

## Anticoagulants 00:13:33

| | RBC life span |
|---|---|
| - Acid citrate dextrose | - ACD -> 21 days |
| - Citrate phosphate dextrose | - CPD -> 28 days |
| - Citrate phosphate dextrose adenine | - CPDA -> 35 days |
| | -SAGN -> 42 days |

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**Citate chelates calcium**

- Phosphate maintains PH
- Dextrose provides glucose
- Adenine helps in ATP synthesis

### Blood bag additives

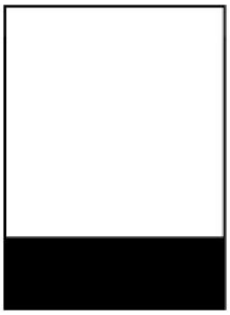
### SAGM sold as Ad sol 1

- Saline
- Adenine
- Glucose
- Mannitol – maintains cell membrane
- Life of RBC with SAGM =42 days

## Complication of stored blood 00:16:56

- Concentration of $H^+$ increase -> s PH decrease
- K $^{=}$increase -> hyperkalemia, hypokalemia can also occur rarely
- O2 content start falling
- High risk of contamination especially by Yersinia enterocolitis (iron loving bacteria)
- Hypocalcemia (citrate chelates calcium)

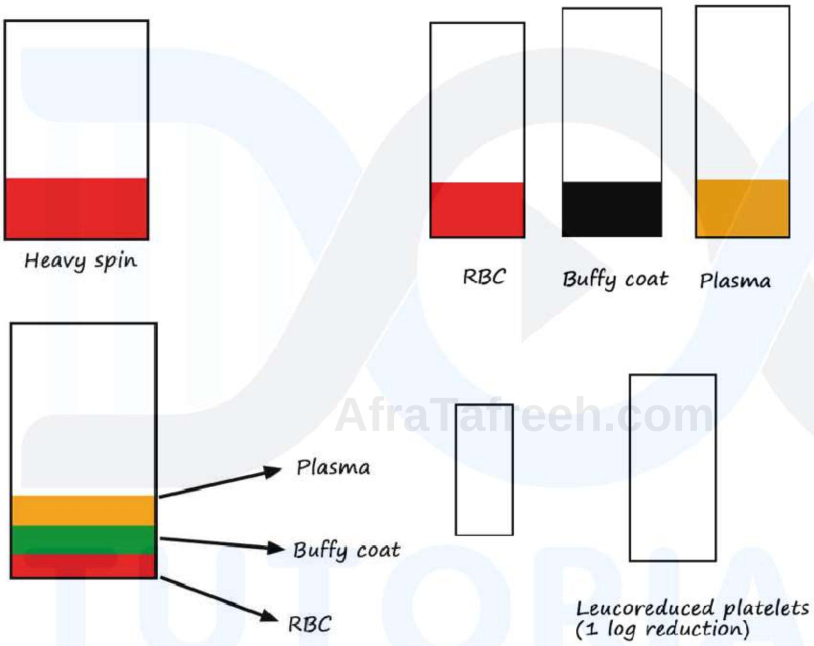
## Platelet concentrate 00:21:10



- Always kept on platelets agitator to maintain viability

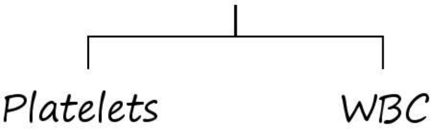
- Viability of platelets is checked by swirling
- Viable for 5 days
- Stored at room temperature 20-24° c
- Platelet concentrate bags are ABO & Rh matched to prevent sensitization platelet agitator

## Quadruple bags: separating leucoreduced platelets


Heavy spin
RBC
Buffy coat
Plasma
Plasma
Buffy coat
RBC
Leucoreduced platelets
(1 log reduction)

- Buffy coat platelets are better quality platelets
- Platelet increment is better in recipient is better
- Single bag-> whole blood
- Double bag-> PRBC, PRP
- Triple bag -> PRBC, platelets, plasma

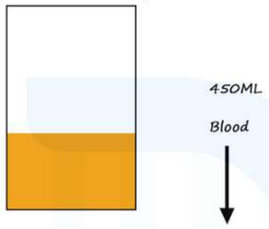
- Quadruple bag-> PRBC, buffy coat, plasma


Platelets
WBC

- Quadruple bag with internal filter –. Leukoreduction is better & reaction are less
- Leukoreduction filter: WBC levels < x 10 ⁶ leucocytes
- i.e.,3 log reduction reduced risk of CMV infection

## Random donor platelets& single donor platelets

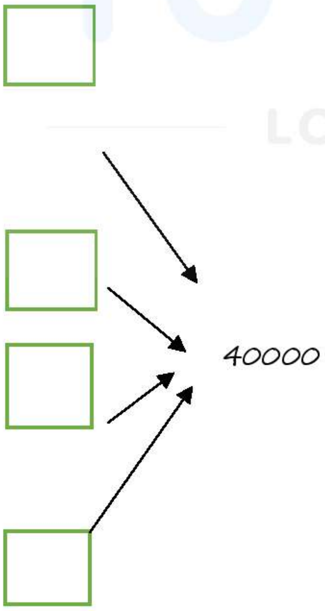
RDP SDP



Involves apheresis of blood from single donor
- Gives appo 200 ml platelets
- Increment of 50000 –* 60000

51;48 Apheresis machine

- Gives 50–70ml platelets
- Increment in platelet level is only by 10000
- To increase platelets, count by 4000, 4 bags of RDP needed



- Only one person platelets are transferred
- It equivalent to 6 RDP bags
- Called JUMBO bag
- Exposed to only one person to only one person's
- So, SDP are preferred over RDP

Patients is exposed to antigen from 4 different donors so antibodies develop against antigen from various donors and patient stops responding to platelets bags this called platelets refractoriness

Red cells
Concentrate
PRBC
Het 65-75%

## Plasma

- has to be frozen within 6 hrs. of collection because t ½ of factor VII is 6 hours labelled as fresh frozen
- stored at 18° c for 1 year
- always ABO matched

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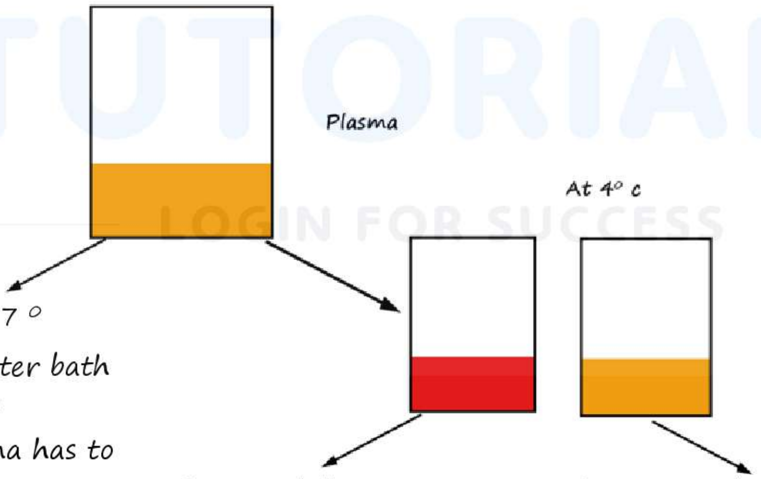


At 37 °
In hot water bath
↓
This plasma has to
Be used with in
24 hrs.

Cryoprecipitate
- Cryo mans at cold so precipitate
- Rich in factor 8
- VWF
- Fibrinogen
- Factor 13
- Fibronectin

Cryo poor plasma
- No WF
- only indication thrombotic thrombocy topenia purpura
 - TTP

- Albumin concentrates are derived from plasma

| Components in quadruple bags | SAGM | temperature |
|---|---|---|
| PRBC | 42 days | 2-6° |
| Platelets | 5 days | 20-24 ° |
| Plasma | 1 year | - 18 ° |

## Special bags

Washed RBC

- Transferred inRecipients withDeficiency
- All non-specificAntibodies stuck To RBC are removed
- Life span of RBC Reduced to 24 hrs After washing

Irradiated blood

- Radiation make T cells impotent
  ↓
- so they do not secrete cytokines person does not develop GVHD
- Blood transplant patient or immunocompromised patients
- Shelf life 28 days

Frozen

- Glycerol used to freeze RBC
- lifespan becomes 10 years
- Done for rare group

## Update

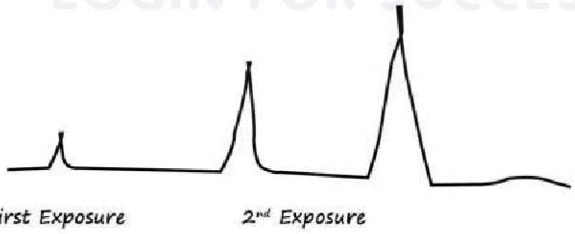
Artificial blood -2 main categories of oxygen carrying blood substitute in trail

- Hemoglobin based $O^2$ carriers
- Perfluorocarbon based $O^2$ carriers

- Hb- Hemopexin so Hemopexin levels decrease
- Hb – Albumin

Methemoglobin level increase detected by SCHUM test

- Most common cause of AHTR is Abo incompatibility due to clerical errors, Technical errors
- Clerical Errors
  i. First complaint – Tingling at site o cannula
  ii. Oozing
  iii. Severe Back pain
  iv. Shock
  v. Renal Failure
  vi. DIC



- Sensitization - Aggressive Hemolysis
- Spherocyte formation - Jaundice developing 3-7 Days after Transfusion

# Acute Immune Mediated Non-Hemolytic Transfusion Reaction

FNHTR | allergic | TRALI | Anaphylactic

**FNHTR**

- M/c transfusion reaction
- Fever > 38 °c or More than 1 ° Rise in temperature
- Along with chills and rigors
- Most common causes is presence of antibodies against leukocytes. In donor blood or storage of blood for prolonged duration Ab WBC

↓

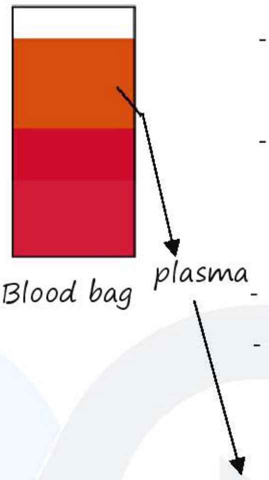
Release of cytokines

$IL_1$, $IT_8$

↓

Fever

**allergic**



**Anaphylactic**

- Usually seen in patients with IgA deficiency
- Formation of Anti – IgA Antibody in recipient post Transfusion
- Anaphylaxis like reaction
- Prevention: Give washed RBC to patients with IGA Deficiency

Release of Histamine bind with IGE bound to most cells in the recipient

↓

Release of Histamine

(Type 1 hypersensitivity reaction)

C/F: chills, Rigor, Purist, Rashes

- So Leukoreduced blood (<=$5x10^6$ WBC's) is preferred in Patients undergoing repeated Blood group Transfusion
  - Caused by activation of Recipient Neutrophils by Donor – derived antibodies Targeting Human leukocytes Antigen (HAL) or Human Neutrophil antigen

- Occurs usually when blood is trans fused Multiparous Female or patients take undergo repeated Blood Transfusion

↓

Ab in plasma of Donor's Blood

Neutrophils | HLA

↓

Release of Granules

↓

Endothelial Injury

↓

ARDS

↓

Hypoxemia

- TRALI usually occurs after Plasma products PRP>>>FFP
- Manifests within 6 hours of Transfusion

## Criteria of TRALI or Possible TRALI

1. TRALI
   a. Documentation of Acute Lung Injury
      i. Acute onset
      ii. Hypoxemia
         - $PaO_2/FiO2 <= 300$
         - $SpO_2 < 90\%$ on Room air
      iii. Bilateral infiltrates on chest x-ray
      iv. No Evidence of circulatory overload
   b. No pre- existing ALI before transfusion

c. During or within 6 hours Transfusion
d. No Temporal Association to an alternative risk factor for ALI

## Criteria of possible TRALI

- Criteria for TRALI plus a Clear Temporal Associated to an alternative factor for ALI

# BLOOD TRANSFUSION PART – I

Blood Transfusion Reaction

- Immune
  - Acute Occurs with in 24 hours of Transfusion
    - **Hemolytic**
      - Acute Hemolytic transfusion reactions
      - Lethal Reaction's
    - **non-Hemolytic**
      - TRALI (occurs within – 6 hrs of transfusion
      - Febrile Non-Hemolytic transfusion Reaction – Most common Transfusion reaction
      - Allergic Non-Hemolytic Transfusion rection
      - Anaphylactic
  - Delayed After 24 hours of transfusion
- Non- Immune
  - **Acute (< 24 hrs)**
    - i. TACO – Transfusion Associated Circulatory Overload
    - ii. Hypocalcemia
    - iii. Acidosis
    - iv. Hypocalcemia commonly in Apheresis or mawire Transfusion
  - **Delayed (>24hrs)**
    - i. Transfusion transmitted Infection
    - ii. Transfusion associated Hemoriderous (TAS) – in patients receiving repeated Blood transfusion

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## Hemovigilance 00:06:00

- Steps followed from procurement till transfusion Blood to patient to prevent Transfusion reaction

## Immune Mediated Delayed Transunion Reaction

00:09:19

- Post transfusion Purpura (> 7-10 days averter transfusion)
- Delayed Hemolytic Transfusion Reaction
- Transfusion associated GVHD

### Hemolytic Transfusion Reaction

Hemolytic Transfusion Reaction

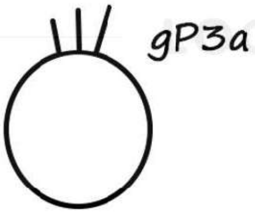
| **Acute (AHTR)** | **Chronic (CHTR** |
|---|---|
| • Main antibody -IgM<br>↓<br>activation of Complements<br>activation of membrane attack complex<br>↓<br>lysis RBC IN circulating acute IVH<br>Hemoglobinemia  hemoglobinuria | • Main Antibody - IgG formed against specific Blood group - Rh, Kell, kid, Duffy<br>Enter Spleen - Results in decreased surface of volume ration of RBC's<br>↓<br>Spherocyte formation |

| | |
|---|---|
| • Free Hb binds with Haptoglobin so levels of Haptoglobin decreases | • IgG antibodies shows Amnestic Response 3-7 days after Transfusion |

- NAT Test reduces window period

## Immune Delayed Transfusion Reactions

- DHTR
- Because of IgG antibodies formed
- Against Rh, Kell, Duffy, Kid

| Post Transfusion Purpura | Transfusion associated GVHD |
|---|---|
| - Because of anti – HPA -1 (Human platelets antigen) Antibodies<br>- Directed against Gp3a of platelets<br> <br>- Occurs after 7 days of transfusion | - Because transfusion to immunocompromised person<br>- Pretext T cells from Donor Blood Damage<br>Skin ↓ Rash<br>GIT ↓ Diarrhea<br>Liver ↓ Jaundice |

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## Work-up of Transfusion Reaction

i. Immediately stop Transfusion

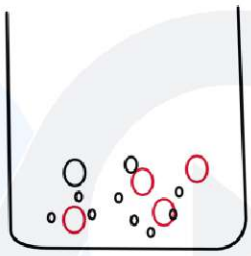
ii. Collect Urine sample of patient

iii. Collect Blood in 2 vials – RDTA vial
- Serum vial

– To send for Biochemical investigation & to Blood Bank

Increase LGH levels
Bilirubin
Methemoglobin decrease
Haptoglobin decrease

post Transfusion staple
pre transfusion sample



Look for Antibodies over RBC's by Direct coomb's test

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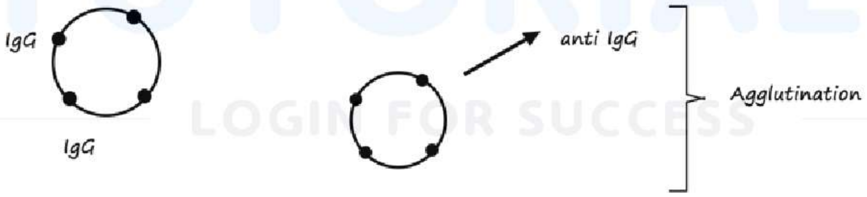
## Direct Coombs Test /Direct Agglutination Test



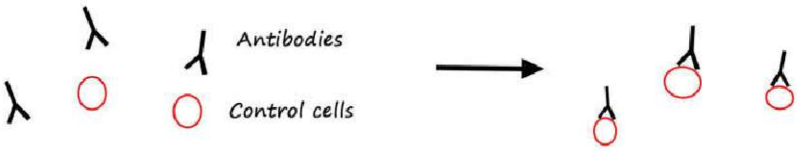
- So, if with coomb's sera tat is anti IgG antibody – agglutination occurs → implies presence of IgG antibody over RBC

## Pre-Transfusion Sample

- Separate RBCs & plasma
- Look for antibodies in plasma indirect coomb's test

## Indirect coomb's Test

- Done when antibodies are suspected in plasma



+

Coomb's Antisera Contains Anti IgG, Anti $c_3b$, $c_3d$

↓

Agglutination

↓

Implies presence of antibodies in Plasma

Gel CARD

Fig: 1

- Gel CARD also Know as column Agglutination Technology quicker method of coomb's Test

# BLOOD TRANSFUSION REACTION PART – II

## Non-Immune Reaction 00:01:06

Non-Immune Reaction → Acute (> 24 hours)

- TACO
- Complication of stored Blood
  - Bacterial Contamination
  - Electrolyte abnormalities

Bacterial Contamination

- Most prone are platelet bags. So, look for viability & color. Change in Platelet bags
- Yersinia Enterocolitica Thrives RBC's
- E- Coli & Pseudomonas infection

Electrolyte abnormalities

- Acidosis
- Hyperkalemia
- Hypokalemia

### Transfusion Associated circulatory Overload (TACO)

- Particularly Susceptible are patients of CHF, pregnant Females in 3rd Trimester
- Rapid Transfusion
- Present with Hypertension, Raised JVP, Pulmonary oedema -Hypoxemia
- Elevated BNP Levels
- Responds excellently to Diaretics

- Seen with multiple transfusion of Plasma products like FFP

## Differentiation of TACO and TRLI

| | **TACO (akin to CHF)** | **TRALI (akin TO ARDS)** |
|---|---|---|
| **Timeline** | < 6 hrs | < 6 hrs |
| **Incidence** | More Common (1-8%) | Rare (<<25) |
| **Risk Factors** | FFP<br>Faster rate of transfusion<br>Age > 70<br>History of CHF or HD<br>Positive Fluid Balance > 3L/day | PRP> FFP>PRBCs<br>Presence of antibodies in Plasma |
| **Signs** | Sign of volume overload<br>Hypertension | Fever (≈ 33%)<br>hypotension |
| **BNP** | >1000 pg/mL | < 250 pg/mL |
| **Treatment** | Diuresis | Don't Diuresis |
| **Prevention** | Decrease Transfusion rates | n/a |
| **Mortality** | 5-15% morality | 5-8% morality |

# Delayed Non-Immune Transfusion Reaction 00:01:06

## Delayed Non- Immune Transfusion Reactions

### Transfusion Transmitted infection

- Viral Infection more common
  - HBV
  - HCV
  - HVA (Rare)
  - CMV
  - EBV
  - HTLV
  - HIV
- Malaria
- Syphilis
- Toxoplasma
- Brucellosis

### Transfusion associated Hemosiderosis

- In patients with multiple transfusion like Thalassemia/ Aplastic anemia
- Present with Iron Overload

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- Testing done by 4th generation ELISHA for HBV, HCV, HIV, Syphilis
- Card Test for Malaria

# CYTOPLASMIC PROTEINS AND IMMUNOHISTOCHEMISTRY

### Normal Cell

- Eosinophilic cytoplasm
- Basophilic nucleus
- Nuclear chromatin

## Cytoskeleton 00:00:05

- Cellular elements that lend shape & form to the cell
- Primarily three filaments
  i. Microtubules
  ii. Microfilaments
  iii. Intermediate filaments

### I. Microtubules

- Hollow fine tubules made up of protein called tubulin.
- They are polar with assembly (polymerization) at one end (plus end) & disassembly (depolymerization) at other end (the minus end)
- They are dynamic portion of cell cytoskeleton
- Function to determine cell shape and cell movements.
- Microtubules are necessary for formation & function of mitotic spindles.

## II.Microfilaments – (5-9.5 nm diameter)00:02:22

- Filamentous structures, made up of two of F-actin (filamentous actin) stands that are coiled helically
- Actin is the most abundant protein in mammalian cells, and is most often associated with muscle contraction
- 2 types of actins
  a. G actin (Globular)
  b. F actin (Filamentous)
- Similar to microtubules, Microfilaments move about by polymerization at one end & depolymerization at other end.
- Microfilaments are abundant in lamellipodia. The processes that cell put out when they crawl along surface.

TUTORIALS LOGIN FOR SUCCESS

## III. Intermediate filaments (diameter 10-12 nm) 00:03:00

- Unlike microtubules & microfilaments, intermediate filaments are very stable & remain mostly polymerized, not undergoing rapid assembly & disassembly & not disappearing during mitosis, as do actin & many microtubules.

- Important exception to this is lamins, which subsequent to phosphorylation, disassembly at mitosis & reappear when it terminates.

## 6 types of intermediate filaments

i. Cytokeratin (epithelial tissue) – carcinoma
   Eg. Squamous cell carcinoma

ii. Vimentin – present in fat cells endothelial cells, smooth muscle, mesenchymal tissue.
   Eg. Lipoma, liposarcomas, endothelial cancers, smooth muscle myomas, melanoma

iii. Desmin – (skeletal muscle) – positive for Rhabdomyosarcoma.

iv. Neurofilament – present in 2 types of tumors
   A. Neuro-endocrine tumor (NET)
      a. Carcinoid
      b. Pheochromocytoma
      c. Neuroblastoma
      d. Small cell carcinoma lung
   B. Neuronal tumor of Brain
      a. Ganglioglioma
      b. Gangliocytoma
      c. Neurocytoma

v. Glial fibrillary acidic protein (GFAP)
   - Positive for Glial tumors of brain
      a. Astrocytoma
      b. Ependymoma

c. Oligodendroglioma

vi. Lamin (A, B, & C) – In nuclear lamina.

## Applied pathology

- Intermediate filament, Lamin present in Nucleus is derived from genes LMN (A, B & C)
- Acquired mutation of Gene LMN (A)  No synthesis of lamin which result in premature aging (progeria)
- This syndrome is called as Hutchinson Gilford Syndrome.

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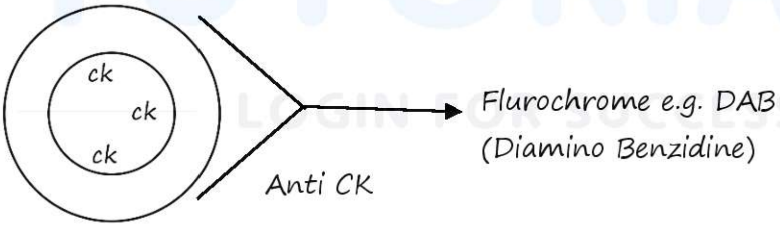
## Immunohistochemistry 00:12:46

- Artificial antibody covered with fluorochrome. Ab

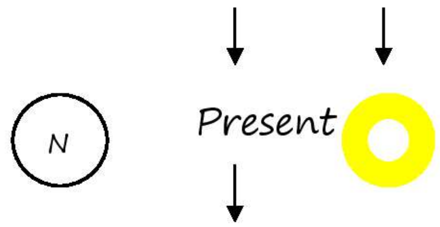
↓

Target – Tumor tissue

(antigen)


ck
ck
ck
Anti CK
Flurochrome e.g. DAB
(Diamino Benzidine)

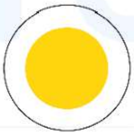
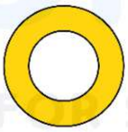
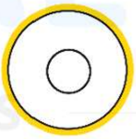
- Basis – Intermediate filaments



DHC staining patterns

- If high in a cell EM increase Hallmark of cell injury
- Cytoplasmic
- Membranous

Nuclear pattern 00:22:40

| | | |
|---|---|---|
|  |  |  |
| E.g –<br>i. Steroid hormone receptors<br>- ER, PR<br>ii. Ki – 67 (mitotic activity marker) | i. Cytokeratin ck<br>ii. Vimentin<br>iii. Desmin<br>iv. S100 | i. Her 2 Neu. |

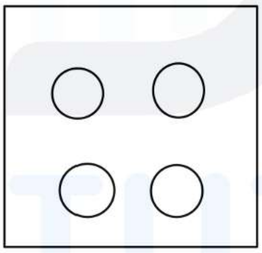
iii. HMB45 ┌ (Melanin specific marker)
└ Pecoma

iv. TTF-1

Thyroid Transcription Factor – 1

(Positive in adenocarcinoma lung)

- S100 positive tumors
  - i. Neural tumors – Schwannoma, Neurofibroma
  - ii. Melanoma
  - iii. Cartilagenous tumors
  - iv. Histocytic tumors Eg; Langerhans cell histiocytosis LCH.



Membranous pattern of staining in her 2 Neu positivity

## Scoring of HER-2 Immunochemistry Arrays

- Based on intensity and percentage of membrane positive cells, giving a score of 0 to 3+

  3+ = positive her 2 neu (circumferential complete staining in >10% of tumor)

  2+ = Equivocal – Require confirmation with FISH

  1+/0 – Negative.

# FLOW CYTOMETRY

Flow Cytometry
↓
Measuring the cells which are flowing

- Immunophenotyping is done (IPT)
- Antigenic profile of cell can be identified

## Procedure 00:02:01

- Done by a machine called flow cytometers
- A laser light is projected on flowing cells in a tunnel with sheath fluid
- When light falls on the cells light get scattered in two directions
  1) Forwards scatter- this happens due to the characteristics of cell size
  2) Side scatter

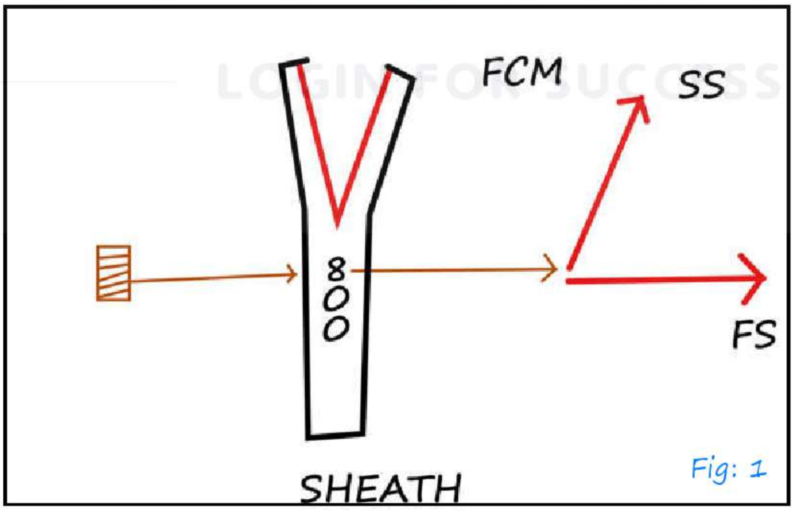


Fig: 1

- Forward scatter α size of cell
- Side scatter α granularity

- CD45 or LCA – Ag present on all mature hematolymphoid cells
- Create – Abs against CD45 and tag with fluorescent dyes
  - FITC – Fluro Iso Thio Cyanate – Green
  - PE – Phyco Erythrin – Red
- Computer gives results in the form of plots
- First graph to follow is $CD_{45}$ – $SS_c$
- All mature lymphocytes →

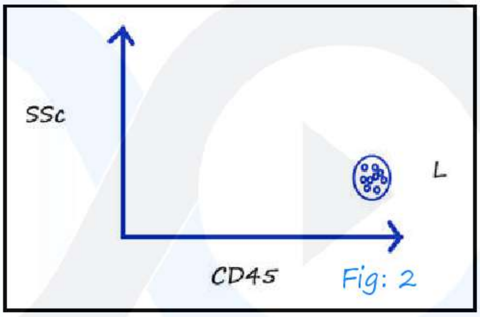


Fig: 2

- All mature neutrophils →

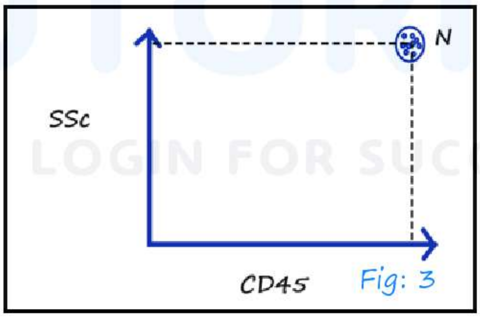


Fig: 3

- Lymphoblasts →
  Dims CD45 positivity

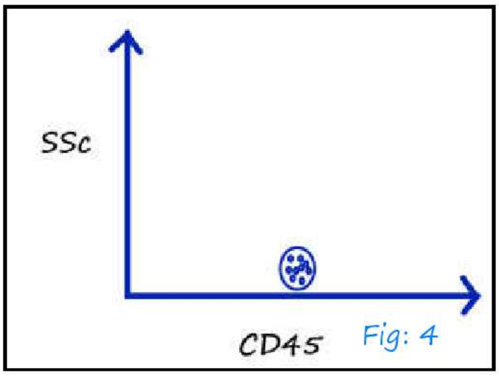


Fig: 4

- Myeloblasts

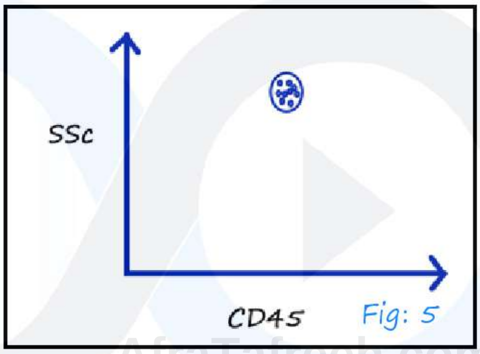


Fig: 5

## Protocol for all 00:14:24

| | |
|---|---|
| Immature Marker (1st) | Mature Marker → For Lineage (2nd) |

**Example:**

First identify lymphoblasts by using TdT as an immaturity marker then classify them into B or T lymphoblasts using specific mature markers.

- CD19 – Pan B cell markers
- Strong CD19 – it's a B cell
- Weak CD19 – Check for
  - CD20, CD79a

(or)

- CD10, CD22

- CD3 – pan T cell marker
- CD1-8 – T cell marker
- TdT, CD3, CD4 positive? Ans: T ALL
- TdT, CD19 CD10 positive? Ans: B ALL

## Protocol for AML 00:19:57

- Immaturity marker: HLA DR
- Most immature stem cell marker: CD 34
  - Granulocytic lineage → MPO, CD13, CD13, CD33
  - Monocytic lineage → CD11c, CD15
  - Erythrocytic lineage → CD71
  - Megakaryocytic lineage → CD41, 42, 61
- APML – Promyelocyte → negative for CD34 HLA DR immaturity markers
- Example: MPO, CD34, CD13, CD33
  HLA DR, CD10 → AML with Aberrant CD10 positivity
- Example: CD19+, TdT +
  CD13+, CD33+ → All with Aberrant myeloid antigens
  ↓↓
  Seen in ALL with t(9,22)
- Example: CD19+ TdT+ CD34+, MPO+
  CD13+, CD33+ → Biphenotypic Leukemia

## Identification of B-ALL 00:28:17

CD19 ⊕
- Pro B ALL → CD34, TdT, CD19
  ↓
- Common → CD10 (Good prognosis) → common ALL Ag (CLLA)
  ↓
- Pre-B ALL → Cytoplasmic μ
  ↓
- Late pre-B/Mature → ⊕ surface IgM

## Images 00:31:20

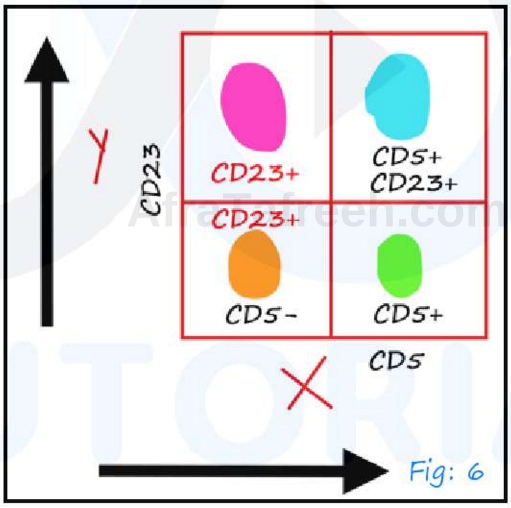
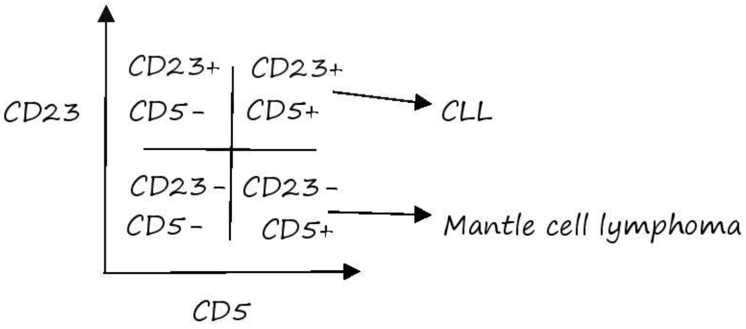

Y
CD23
CD23+
CD5+
CD23+
CD23+
CD5-
CD5+
CD5
X
AfraTafreeh.com

Fig: 6


CD23
CD23+
CD5-
CD23+
CD5+
CLL
CD23-
CD5-
CD23-
CD5+
Mantle cell lymphoma
CD5

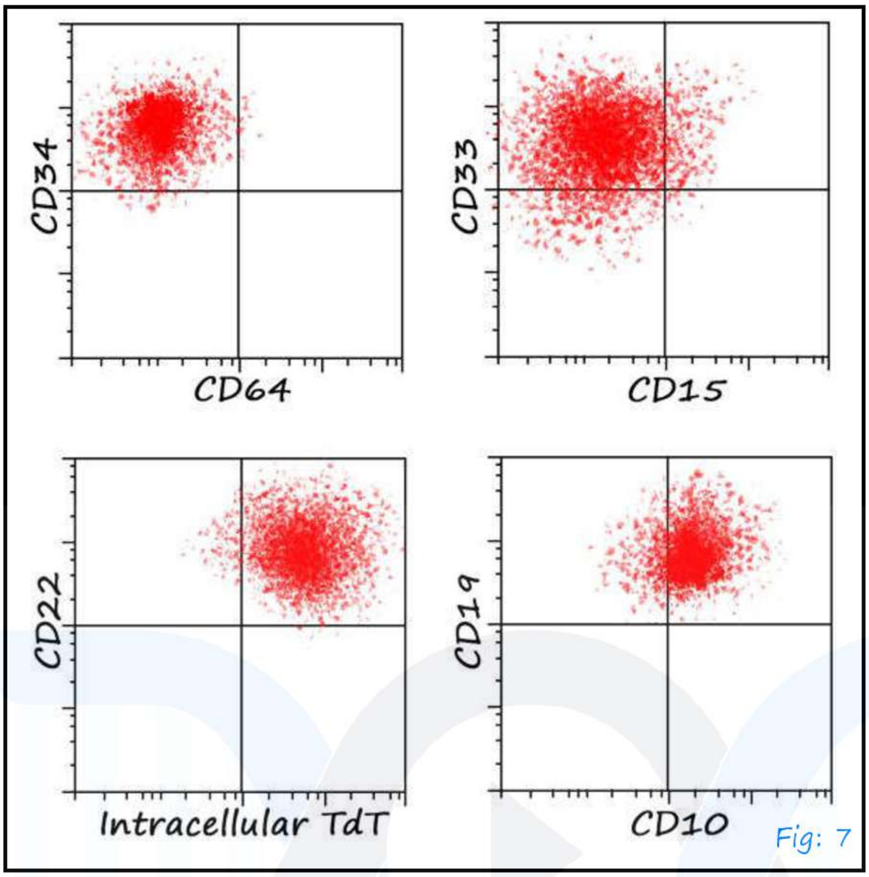


Fig: 7

# HISTOPATHOLOGY FIXATION

## Techniques 00:00:15

- Histopathology
- Fixatives
  - To preserve the structure (morphology)
  - Makes tissue harder & easier to cut

## Types of fixatives 00:02:24

Types of fixatives

Physical
↓
Heating: Microwave
Freezing with liquid N2

Chemical
↓
- Coagulant: e.g.: Alcohol, acetone → Dehydrate the tissues
- Cross linking: e.g.: Aldehyde metal salts → of proteins
- Compound e.g.: Alcoholic formalin

AfraTafreen.com
TUTORIALS
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- Best: 10% buffered neutral formalin fixation

↓
Made by
Formaldehyde (40% → 10%)
↓
Add buffered salts ($Na_2H$ $Po_4$, $NaH_2Po4$

↓
PH: 7.2 – 7.4
↓
>6
↓
Formalin pigment

- Coagulative fixation used for cytopathology
- Cross linking aldehyde fixations: Preferred for histopathology

## Formalin pigment 00:08:59

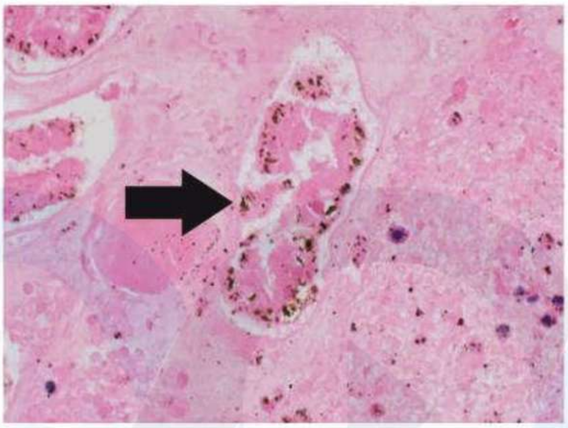

Fig: 1

- Can be confused with hemozoin (From malarial parasite)
- Remove formation by alcoholic sol of picric acid

## Glutaraldehyde cross linking 00:10:43

- Osmium tetraoxide can also be used for EM
- Coagulant fixative

**Cytology:**

- Pap smear 95% ethanol
- Exfoliative cytology → Giemsa stain can be used e.g.: BAL, gastric lavage no fixative in necessary air dry
- Pap stain: Better for sewing nuclear morphology

## Bouin's fixative 00:15:32

- Was used for cell blocks
- Now used for testicular

Fig: 2

- Has picric acid, acetic acid, formaldehyde

## Carnoy fixative 00:18:10

- Contains chloroform (30%) + Ethanol (60%) + Glacial acetic acid (10%)
- Fixative of choice for karyotyping

## Saccomano fixative 00:21:49

- 50% alcohol + 2% carbowax → Keeps cells viable helps in deloyed transport
- Fixative of choice for exfoliative cytology

## Difference in fixatives 00:24:39

| Bouin`s | Saccomano | Carnoy |
|---|---|---|
| ↓<br>Yellow<br>P, A, F<br>↓<br>Testicular biopsy | ↓<br>50% ethanol<br>+<br>2% carbowax<br>↓<br>Exfoliative cytology | 60% ethanol<br>30% chloroform<br>10% GAA<br>↓<br>Karyotyping |

- Formalin fixative artifacts
  - Orphan arvie eye nucleus in papillary Ca. of thyroid
  - Lacunar cells in nodular sclerosis type of Hodgkin's lymphoma
  - Fat dissolves